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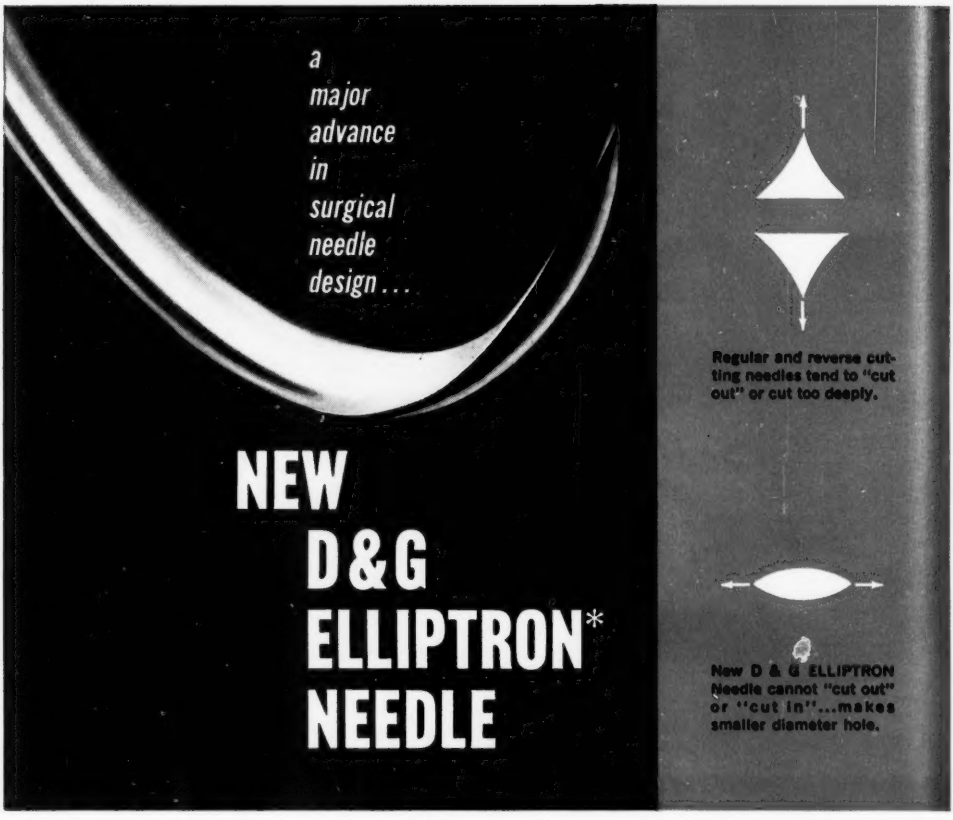

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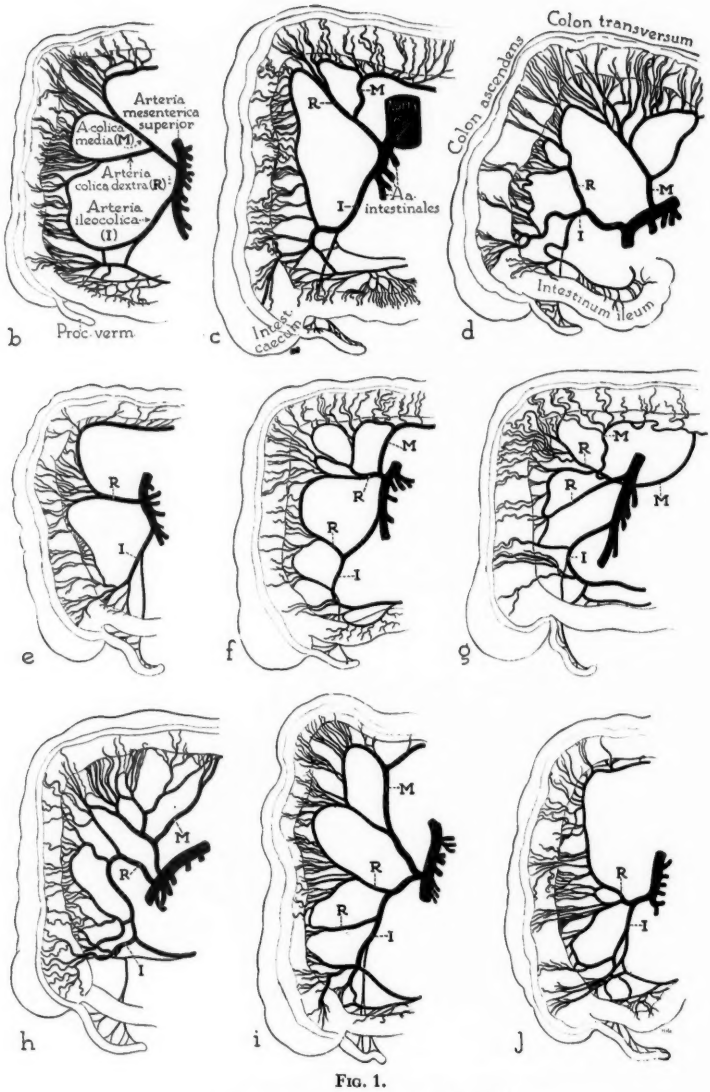

FIG. 1.

(*See page 387 for Figure 1a and legend.*)

Surgical Anatomy of the Arterial Supply to the Colon from the Superior Mesenteric Artery Based upon a Study of 600 Specimens.—*John Sonneland, Barry J. Anson, and Lindsay Beaton.*

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SURGICAL ANATOMY OF THE ARTERIAL SUPPLY TO THE COLON FROM THE SUPERIOR MESENTERIC ARTERY BASED UPON A STUDY OF 600 SPECIMENS

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MORE THAN A CENTURY has passed since the publication of Richard Quain's *The Anatomy of the Arteries of the Human Body*. In the preface to this classic he wrote:

> The difficulties which have often occurred in the performance of those surgical operations in which the larger arteries are concerned have arisen in great part from want of sufficient acquaintance with the differences in anatomical disposition to which these vessels are subject.

Yet, the surgery of the middle years of the nineteenth century demanded so little knowledge of precise visceral anatomy that in Quain's study of 1,040 bodies the colic arteries are merely named, without note of "the differences in anatomical disposition to which these vessels are subject."

It seems an unusual circumstance that, despite the dramatic advances in the field of intestinal surgery during the period of 114 years, our present-day textbooks are pictorially no better than Quain's great folio volume published in 1844. It is true, of course, that the literature contains frequent references to aberrant colic arteries—an interesting subject, but not one of vital surgical significance. Only an occasional study, such as the 1933 report of Steward and Rankin, has dealt with the applied anatomy of the colic arteries, thus to make a valuable contribution to the surgeon's appreciation of this aspect of vascular morphology.

Although it is generally recognized that the colic arteries do not follow a set pattern, no large scale study heretofore has been reported, which would provide, on statistical bases, predictable probability in occurrence of the several types of arterial supply to the large intestine.

This article, drawing on our experience with 600 cases, will provide a statistical basis for predicting the probability of variation of the colic arteries. Thus, we will demonstrate

Contribution No. 628 from the Department of Anatomy, Northwestern University Medical School, Chicago.
The reported observations were collected over a 15 year period during which William C. Bishop, Myron C. Close, Edmund C. Colton, Ronald G. Haley, David K. McAfee, Robert G. Siekert, and L. Lake Swigart contributed to the accumulation of data for this study.

statistically that the classical pattern of colic arteries is present in but 23.8 per cent of our 600 cases. It will be established that variants of the classical pattern are the rule, not the exception. As we know during surgery, variants for the individual patient are not merely interesting anatomic facts, but may be a matter of life and death. In writing about surgery of the colon, Mayo (14) emphasized this point: "One cannot operate with implicit faith equipped only with a textbook picture. Many, and sometimes tragic, are the lessons learned from experience." The term "anticipatory variants" aptly describes the central thought of this article. Study and knowledge of "anticipatory variants" of the arterial supply to the colon, we believe, should be of material aid to the operating surgeon.

The importance of the blood supply to the colon is emphasized by a mere enumeration of some of the problems facing the present-day surgeon: colon segments for bladder or gastric pouches, inferior mesenteric artery ligation during aortic grafting or left hemicolectomy, suture-line viability problems, and the multiple problems of resection for carcinoma. For example, the American Cancer Society estimates that about 42,000 cases of cancer of the colon are first brought to medical attention each year in the United States. It is at once apparent that if surgery is to fulfill its maximum promise in this field alone, it must be undertaken early and must be complete. Completeness will include not only removal of the local tumor, with containment of intraluminal, transmural, and vascular emboli, but also of the elements of lymphatic drainage, the pathways of which match those of the arteries of supply. Necessarily, an understanding of the variants of arterial supply will aid in achieving maximal tumor removal consistent with minimal surgical trauma. We trust that this article will also add to the surgeon's knowledge in such matters as the importance of the marginal artery in the absence of the middle colic artery, significance of the accessory middle colic artery during gastrectomy, anticipated problems of suture line viability depending on variable vascular morphology, and perhaps on other problems which we cannot presently foresee.

MATERIAL AND METHODS

Regular dissection-room specimens were used for the present study. Most of the subjects were white males. The origins and interrelationships of the ileocolic, right colic, and middle colic arteries were studied as encountered in a total of 600 bodies. Twenty-four patterns were found, which, for purposes of more graphic presentation and readier comprehension, are placed into 7 types, each of which is based on absence or reduplication of constituent arteries. It is readily apparent, then, that the familiar arterial pattern of the textbooks (Fig. 1a) is but one of many variations, itself accounting for a minority of specimens encountered in the study (Figs. 1, 2, and 3).

Fourteen especially favorable specimens were studied in order to determine the variation in arrangement of the terminal arteries to the mesenteric border of the colon.

OBSERVATIONS AND DISCUSSION

The familiar textbook description assigns 3 major branches from the super mesenteric artery to the colon. Those of our series which fall into this category we have placed in type I: a single tributary directed from the superior mesenteric artery toward the ileocecal area, the ascending colon, and the transverse colon (see Fig. 2). Of the 600 specimens, 68.0 per cent (408 bodies) possessed some specific type of this generic pattern. Type I naturally divides into 3 parts, each of which represents about one-third of the type. The first subdivision (type Ia) is the classic textbook pattern: the superior mesenteric artery gives rise in succession to the middle colic, right colic, and ileocolic arteries (23.8 per cent; 143 specimens). The second (Ib) varied only in having a common stem from the superior mesenteric artery for the right colic and ileocolic arteries (22.7 per cent; 136 specimens). In the third

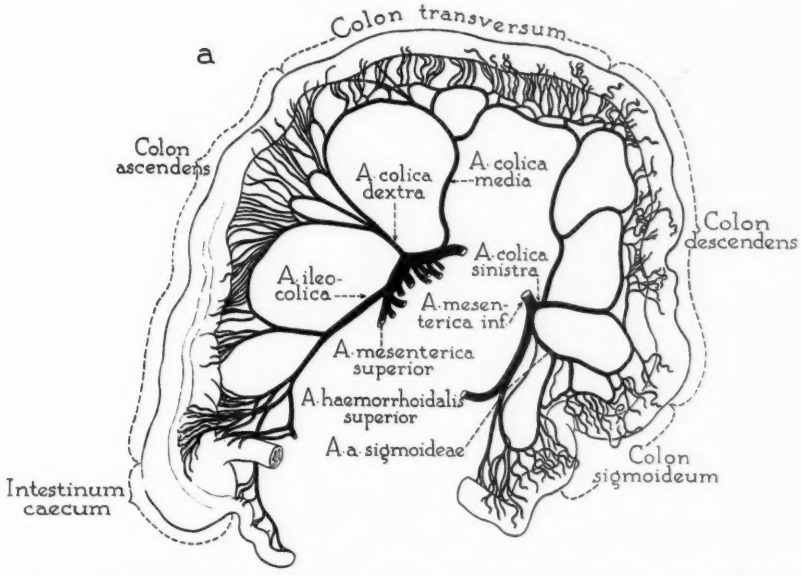

FIG. 1. a, Above; b to j, facing page 385. Arterial supply to the colon from the superior mesenteric artery. Types selected from 125 specimens. Drawings prepared from original dissections. Abbreviations: *I*, ileocolic artery (A. ileocolica); *M*, middle colic artery (A. colica media); *R*, right colic artery (A. colica dextra). a, Commonest pattern of mesenteric branching, in which the middle colic, the right colic, and the ileocolic arise separately; occurring in 23.8 per cent of 600 specimens (see Fig. 2a). b and d, Two other common patterns of division, in each of which 2 of the 3 regularly named branches arise from a single mesenteric root (being similar to those shown schematically in Figs. 2b and c), and which with the type pictured in Figure 2a, make up a total of 60 per cent of 600 specimens. c, Representing a variant of Figure 1b, the intermediate member of the triad of vessels reaching the digestive tube in the area of junction of the transverse and the ascending portions of the colon rather than at the latter segment. e, A system of branching in which a middle colic is wanting. f to h, Variation in the derivations of 2 vessels of mesenteric origin, with early subdivision into multiple rami of relatively great caliber. i and j, Examples of colic supply through a single artery of mesenteric origin; in Figure 1e, 5 vessels of considerable caliber spring from the single source, whereas in Figure 1j only 2 are so derived.

subdivision (Ic), the superior mesenteric artery is the source of a common stem for a right colic and a middle colic artery, and for a separate ileocolic artery (21.5 per cent; 129 specimens).

The second major type (type II) is distinguished by the absence of the right colic artery: 12.4 per cent of the cases (74 specimens) fell into this category. In the first subdivision (IIa) the superior mesenteric artery produced 2 vessels, an ileocolic and a middle colic artery (10.5 per cent; 63 specimens). Those of the second subdivision (IIb) differed only in possessing an accessory middle colic artery (1.7 per cent; 10 cases), while the third (IIc) was identical save for the occurrence of a common stem origin for the ileocolic and one of the middle colic arteries (0.2 per cent; 1 case).

The third type (type III) shows absence of the middle colic artery (3.6 per cent; 22 specimens). Single ileocolic and right colic arteries arose directly from the superior mesenteric artery in the first subgroup, IIIa (2.8 per cent; 17 cases), and by a common stem in the second (0.8 per cent; 5 cases).

Specimens of the fourth major type (type IV), with more than 1 right colic artery, were fairly common (8.9 per cent; 53 specimens). In the first subgroup (IVa) the su-

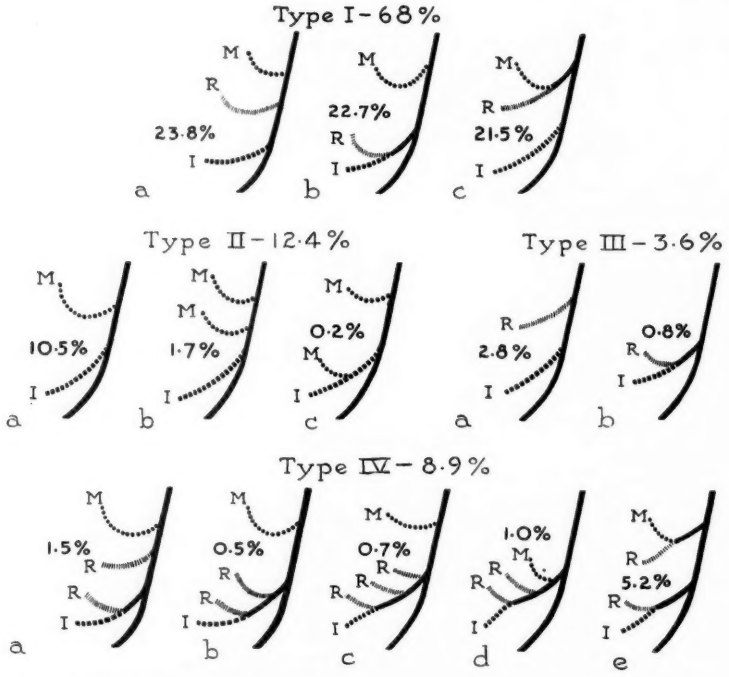

FIG. 2. Types of colic branching of the superior mesenteric artery and varieties within each of 4 categories (types I to IV). Schematized from records on 600 specimens. Abbreviations for arteries: *I*, ileocolic; *L*, left colic; *M*, middle colic; *R*, right colic.

perior mesenteric artery gave rise to a common stem for an ileocolic and a right colic, to an accessory right colic and to a middle colic artery (1.5 per cent; 9 specimens). In the second subgroup (IVb) a middle colic, a common stem for ileocolic, and 2 right colic vessels arise from the superior mesenteric (0.5 per cent; 3 specimens). In the third (IVc) there were 3 right colic arteries (0.7 per cent; 4 specimens). In the fourth subgroup (IVd) a common trunk arose from the superior mesenteric artery to produce successively a middle colic, and a right colic, then to divide terminally into an ileocolic and a second right colic artery (1.0 per cent; 6 specimens). The fifth, and final, subdivision (IVe) was characterized by 2 common stems, from one of which originated a middle and a right colic, from the other of which originated a second right colic, then an ileocolic artery (5.2 per cent; 31 specimens).

The fifth major type (type V) (6.2 per cent; 38 specimens), each specimen of which contained 2 or 3 middle colic arteries, includes specimens of 8 patterns, not counting those previously listed as type IIb and c. In the first and second subdivisions within this type, 2 middle colic arteries arose from the superior mesenteric artery, with a right and an ileocolic artery present: the latter vessels arose from the superior mesenteric artery in Va (0.2 per cent; 1 case), and from the same artery by a common stem in Vb (1.8 per cent; 11 cases). In the third subgroup (Vc) a middle colic artery arose not only from the superior mesenteric artery, but from a common trunk, producing also the right and ileocolic vessels (0.3 per cent; 2 specimens).

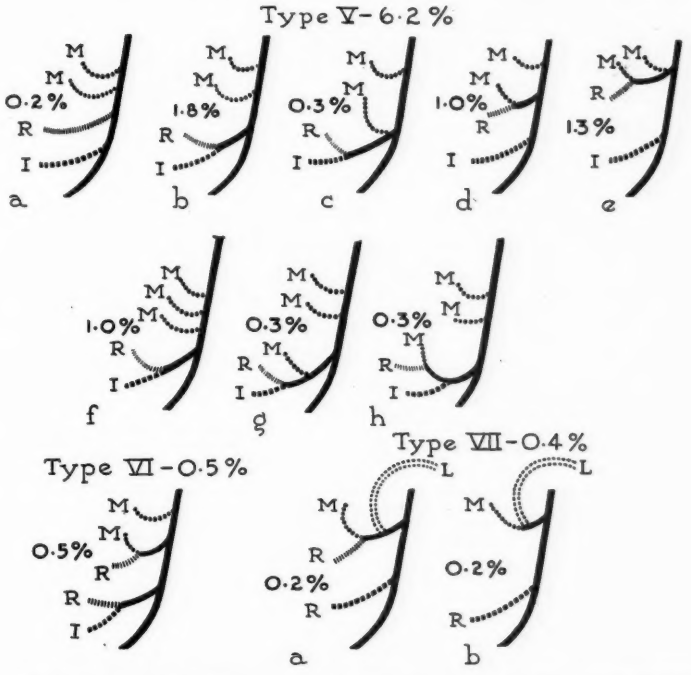

FIG. 3. Variations in the arterial supply to the colon from the superior mesenteric artery, continued, (types V to VII). In type I (representing 68 per cent of all specimens studied), the 3 typical branches, of approximately equal caliber, arise either independently from the superior mesenteric, and thus as 3 vessels, or from 2 roots (with the right colic derived from ileocolic or middle colic). In type II (12.4 per cent) a right colic artery is wanting and the middle colic is either single or double. The distinguishing feature in type III (3.6 per cent) is the absence of a middle colic in the presence of a right colic of either direct or indirect mesenteric source. In the specimens catalogued as belonging to type IV (8.9 per cent) 2 or 3 right colic arteries occur, accompanied in each variety of subtype by both ileocolic and middle colic branches. Type V (6.2 per cent) is characterized by the occurrence of 2 or 3 middle colic arteries in the presence of a right colic (in contrast, type II) and of an ileocolic artery. In type VI (0.5 per cent) both middle and right colic arteries are doubled. In type VII (0.4 per cent) a left colic artery is added to the typical set of 3 branches.

In the fourth division of type V (Vd), a middle colic artery and the ileocolic artery arose directly from the superior mesenteric, while a second middle colic and the right colic arteries were the branches of a common stem (1.0 per cent; 6 specimens), while in the fifth (Ve) a common trunk gave rise not only to the right colic, but to 2 middle colic arteries, the ileocolic arising from the superior mesenteric artery (1.3 per cent; 8 bodies). Three middle colic arteries characterized the last 3 divisions of type V (Vf Vg, and Vh): in Vf the vessels all arose from the superior mesenteric artery, with a common trunk origin of the right and ileocolic arteries (1.0 per cent; 6 cases); Vg differed only in that 1 of the middle colic arteries arose from the ileocolic trunk (0.3 per cent; 2 cases); Vh displayed the same pattern except that 1 of the middle colic arteries arose from a common trunk with right colic off the ileocolic (0.3 per cent; 2 cases).

But a single pattern formed type VI, characterized by multiple right and middle colic arteries (0.5 per cent; 3 bodies). The superior mesenteric artery gave rise to 3 vessels, a middle colic artery, a trunk dividing into middle and right colic arteries, and a final trunk dividing into right and ileocolic arteries.

We found only 2 instances in which a major artery from the superior mesenteric was directed toward the descending colon (type VII) (0.4 per cent). In VIIa the sole supply for the abdominal colon arose from the superior mesenteric artery, the inferior mesenteric artery supplying only the pelvic colon and upper rectum. As shown in Figure 3, a large trunk arose from the superior mesenteric artery, promptly giving origin to the left colic, then dividing into a middle and right colic; an additional right colic artery arose from the ileocolic as the latter terminated (0.2 per cent; 1 specimen). In type VIIb a left colic artery from a common stem origin with the middle colic was supplemented by a left colic arising from the inferior mesenteric artery (0.2 per cent; 1 specimen).

CONSTITUENT VESSELS OF THE COLIC ARTERY SYSTEM

The ileocolic artery. The ileocolic artery, defined as that major colic artery directed toward the cecal area, was present in all 600 cadavers. It arose as a single branch from the superior mesenteric artery in 63.2 per cent of our series. In 36.9 per cent of cases it arose with 1 or more arteries to the right colon by a common stem off the superior mesenteric artery.

In a group of 32 cadavers the superior mesenteric origin for the ileocolic artery was an average of 6.9 centimeters (minimum 5, maximum 9.5 centimeters) from the origin of the superior mesenteric artery (Fig. 4). In the same group the distance from the superior mesenteric artery to the cecal wall, measured along the curving course of the artery, was 15.3 centimeters (minimum 12.5, maximum 21.5 centimeters).

The ileocolic artery traditionally terminates in 5 branches, these being ileal, ascending colic, appendiceal, and anterior and posterior cecal. Variations in the branches as encountered in 200 specimens may be found in the atlas by Anson.

Right colic artery. Inconstancy and variability of the origin, direction, and size of the major artery or arteries to the ascending colon probably accounted for the failure of early anatomists to name and describe the right colic artery. The right colic artery is that major artery, irrespective of origin, which is directed to the ascending colon between the ileocecal junction and the hepatic flexure.

We found the right colic artery absent in 12.6 per cent (75 specimens) of our series of 600 bodies. In the remaining bodies, the right colic artery arose as a single vessel in 78 per cent of cases; in 8.7 per cent of the series there were 2, and in 0.7 per cent 3 right colic arteries.

The mode of origin of the right colic artery was recorded. In only 28.3 per cent of our series was there a direct superior mesenteric artery origin for at least 1 of the right colic arteries. In the remaining 59.1 per cent of our series the right colic artery or arteries arose in company with 1 or several other colic arteries of superior mesenteric origin, namely the ileocolic, middle colic, or left colic artery in various combinations. In those bodies in which there was single right colic artery, the site of origin was: (1) superior mesenteric (26.8 per cent of the total series), (2) a common trunk with the ileocolic (26.3 per cent), (3) a common trunk with the middle colic (23.8 per cent), (4) a common trunk with both ileocolic and middle colic arteries (0.9 per cent), and, (5) a common trunk with both the middle and left colic arteries (0.2 per cent). In 8.7 per cent of the total series two right colic arteries were present, arising from: (1) a common trunk with the middle colic and a common trunk with the ileocolic (5.7 per cent), (2) both the superior mesenteric and a common trunk with the ileocolic (1.5 per cent),

(3) a common trunk giving rise not only to the middle and ileocolic, but to 2 right colic arteries (1.0 per cent), and (4) a common trunk with the ileocolic (0.5 per cent). In 4 bodies (0.7 per cent), 3 right colic arteries were present, these being of one pattern (IVc) in which all arose in a common trunk with the ileocolic artery. The reader interested in further information concerning the absence or origin of the right colic artery will find references in the literature.

In a series of 30 cadavers in which there were 1 or 2 right colic arteries, the distance from the the origin of the superior mesenteric artery to the more proximal right colic artery was measured (Fig. 4). It ranged from 1.5 to 9 centimeters, the average being 6.2 centimeters. In the same series the right colic artery pathway from the superior mesenteric artery to the colic wall was measured, the shorter distance being recorded if 2 arteries existed. The length varied from 8.5 to 22.5 centimeters, 13.9 centimeters being the average.

Middle colic artery. The middle colic artery usually originated from the superior mesenteric artery and passes to the transverse colon, usually near the hepatic flexure.

We found the artery absent in 3.6 per cent (22 bodies) of our series. In 87.8 per cent a single middle colic artery was present, usually passing toward the right portion of the transverse colon; when associated with a superiorly placed right colic artery, the middle colic not infrequently passed toward the middle of the transverse colon. In 7.0 per cent of our specimens 2 middle colic arteries of separate origins were found, while in 1.6 per cent of cases 3 such arteries were evident.

It may be of interest to consider here the importance of the middle colic artery relative to the colon segment which the marginal artery from it and the left colic artery must bridge (i.e., from the hepatic flexure to the sigmoid colon). The mesenteric borders of each division of 34 preserved colons were measured and the distances averaged. They were as follows: ascending colon 16.4 centimeters (minimum 10, maximum 25 centimeters), transverse colon 34.3 centimeters (minimum 22, maximum 48 centimeters), descending colon 14.9 centimeters (minimum 9, maximum 23 centimeters), and sigmoid colon 11.1 centimeters (minimum 6.5, maximum 17.5 centimeters). The middle colic artery contribution to the marginal arcade provides, then, in company with the left colic artery contribution, for the blood supply of roughly two-thirds of the colon.

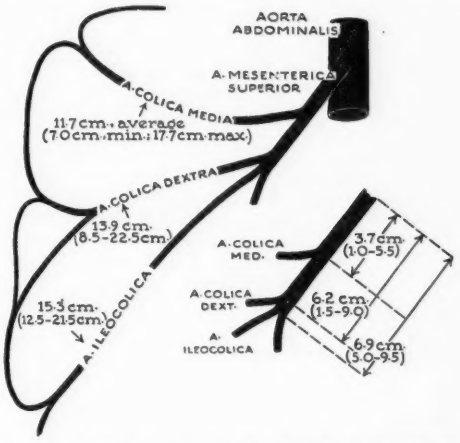

FIG. 4. Variation in length of each of the 3 colic branches of the superior mesenteric artery, recording maximum, minimum, and average measurements; based upon records from 32 specimens.

In those 87.8 per cent of cases demonstrating but a single artery to the transverse colon, 5 sites of origin were noted: (1) directly from the superior mesenteric artery, 59.7 per cent, (2) from a common stem with the right colic artery, 26.7 per cent, (3) from a common stem with ileocolic and right colic arteries, 1.0 per cent, (4) from a common trunk with the right and left colic arteries, 0.2 per cent, and (5) from a common trunk with the left colic artery, 0.2 per cent. The transverse colon was supplied by 2 middle colic arteries in 7.0 per cent of cases, the arteries arising: (1) both from the superior mesenteric artery, 3.7 per cent, (2) from the superior mesenteric artery and from a common stem with the right colic artery, 1.5 per cent, (3) both from a common trunk

with the ileocolic artery, 1.3 per cent, (4) from the superior mesenteric artery and from a common trunk with the ileocolic and right colic arteries, 0.3 per cent, and (5) both from a common trunk with the left colic artery 0.2 per cent. Three middle colic arteries were found in 1.6 per cent of our cases. One per cent showed all arteries arising from superior mesenteric artery, while 0.6 per cent showed 2 arising from the superior mesenteric artery and 1 vessel arising from a common trunk with the ileocolic and right colic arteries. The presence of 2 or 3 middle colic arteries was found in 8.6 per cent of our series. Such multiplicity has been reported in the literature as "anomalous," as has the artery's absence (which we found in 3.6 per cent of cases). We prefer to view the patterns as variants, however.

In 33 cadavers the first artery passing to the transverse colon arose on the average 3.7 centimeters (minimum 1.0, maximum 5.5 centimeters) from the aortic origin of the superior mesenteric artery. It is to be noted that an intrapancreatic origin of the middle colic artery may occur when the artery arises a short distance from the base of the superior mesenteric artery. We could record no instance of an origin other than the superior mesenteric artery system in our 600 specimens. However, the middle colic artery may arise from branches of the celiac axis: Wilson mentions a derivation from the hepatic artery, Henle noted an instance of origin from the splenic artery, Ziegler cites 2 occurrences of origin from the the gastroduodenal artery, while Pierson found 2 cases of derivation from the superior pancreatic artery.

In the group of 33 specimens mentioned in the preceding paragraph, the middle colic artery pathway from the superior mesenteric artery to the bowel wall was measured, the shorter distance being recorded in the presence of 2 middle colic arteries. The length of the pathways ranged from 7 to 17.7 centimeters, the average being 11.7 centimeters. In those bodies which possessed but a single colic artery, bifurcation of the vessel occurred early in each case. The average point of bifurcation was 2.6 centimeters from the vessel's origin (minimum 0.5, maximum 4.0 centimeters).

We found but 2 instances from 600 cadavers in which a major artery to the descending colon arose from the superior mesenteric artery system (type VII). A superior mesenteric origin for a left colic artery has been previously reported twice in the literature.

MARGINAL ARTERY

Paracolic anastomoses between the colic arteries were described in 1803 by von Haller and given the name "marginal artery" by Drummond. Secondary, even tertiary arcades are often seen between colic arteries, these arcades being found at points of major bifurcation of the colic arteries and at the colic flexures. Drummond's term, "marginal artery," would include such arcades according to some authors. Huard set apart those primary arcades which occur at times between the superior mesenteric system and the left colic artery, terming the arcade a "central intermesenteric anastomosis." Huard reported from a collective review of 5 sources 52 instances of "central intermesenteric anastomosis" in 630 cadavers.

It may be well to define the marginal artery as the paracolic vessel of anastomosis between colic arteries from which arise terminal arteries to the colon. The marginal artery usually passes uninterruptedly from the ascending colic branch of the ileocolic artery to the descending limb of the final sigmoid artery. Steward and Rankin noted the failure of anastomosis between ileocolic and right colic arteries in 5 per cent of a 40 case series. Merkel, Lockhart-Mummery, and Robillard and Shapiro have noted the occasional failure of the marginal artery between the middle and left colic arteries. The marginal artery usually describes a succession of paracolic arches, the larger arches in their midsections passing fairly parallel to adjacent colon. Meillere found the artery running within 1 to 3 centimeters of the bowel wall. Steward and Rankin state that the

artery runs nearer the bowel wall in the left than in the right colon, the distance varying from a fraction of 1 up to 8 centimeters.

TERMINAL ARTERIES

Terminal arteries are the final, direct branches of the colic artery system passing from the marginal artery to the mesenteric border of the colon, from which point they penetrate the bowel wall directly (short terminal arteries) or just proximally to the mesocolic taenia (long terminal arteries). The number of terminal arteries show a high degree of variability among bodies. In 14 specimens we counted the terminal arteries arising from the marginal artery together with the number of vessels reaching the mesocolic border of the colon. The number of such arteries arising from the marginal artery parallel to the ascending colon averaged 18.9 (the count ranged from 8 to 26), while a similar count at the wall of the colon averaged 39 (range 14 to 86). Counts along the transverse colon averaged 27.4 (range 17 to 43) along the marginal artery, and 67.8 (range 32 to 124) along the colon segment. The vessel count for the descending sigmoid colon segments averaged 18.4 (range 10 to 46) at the marginal artery and 45 (range 18 to 89) at the wall of the colon. Thus, each terminal artery gave rise on the average to 2 or 3 branches proximal to the colic wall. Also, if one interpolates the average count at the colic wall in terms of length of preserved colon segment involved, it is noted that on the average a terminal artery is found every 4.2 millimeters on the ascending colon, every 5.1 millimeters on the transverse colon, and every 5.8 millimeters on the descending sigmoid segment (measurements of practical importance).

ARTERIAL ANASTOMOSES BETWEEN COLON AND OMENTUM

It is to be expected that little arterial anastomosis would be found between the transverse colon and omentum because, embryologically, the arterial pattern to the colon is established before the omentum adheres to the transverse colon. However, in 1916 Mayo (16) described a rather constant vessel between splenic flexure and omentum, which should be tied when mobilizing the flexure. Subsequently, others commented on vascular bridges between the colon and posterior leaf of the omentum. From experience, the surgeon knows that considerable individual variation exists, some dissections proceeding in a virtually bloodless field, whereas in other cases numerous bleeding points are encountered in separating the omentum from the colon.

SURGICAL CONSIDERATIONS

The surgeon is primarily interested in an anatomic study such as this from the aspect of practical operating room applications. The present study, which has been a continuing research effort in the Department of Anatomy at Northwestern University since 1937, certainly has important implications for surgery as we now know it. What future value the study will have as our knowledge of surgery advances, nobody can accurately predict.

Cancer remains the most challenging aspect of surgery of the colon. Until about a decade ago our thinking was essentially directed toward extirpation of the gross tumor and of its lymphatic extensions. In the last few years striking contributions have been made in 2 areas of colic surgery. First, the extent of lymphatic resection has been broadened, for reasons soon to be discussed. Secondly, cytologic studies have been published indicating heretofore unsuspected avenues of metastases.

Today, then, a fascinating series of new concepts has arisen in the field of cancer surgery: showers of cancer emboli sweep through the venous return as a result of tumor mobilization; recurrence at the line of colic anastomosis occurs, probably due to inclusion of intraluminal cancer cells within the suture line; malignant cells are shed into the peritoneal cavity following transmural tumor penetration; intramural extension of malignancy is found as much as 10

centimeters distal to the gross tumor; and there is an increasing awareness of the threat of multiple polyps and secondary carcinomas, with the concomitant use of coloscopy.

Coupled with the advances just cited is the continuing effort to understand better the avenues of lymphatic extension. A time chart of our knowledge of lymph node metastases would include the anatomic study by Jamieson and Dobson in 1909 in which they defined 4 groupings of colic lymph nodes (epicolic, paracolic, intermediate, and main group) and indicated that cancer could skip metastasize directly to the intermediate or main group nodes. In 1941 Coller, Kay, and MacIntyre noted that the gross impression of nodal invasion was often incorrect, emphasized that every case should be treated as though nodal metastases had occurred, and stated that in general the artery of supply to a colic cancer was the pathway of lymphatic spread. In subsequent years evidence that wide resection is directly related to markedly improved 5 year survival statistics are the several series comparing cancer resections of the right as compared to the left colon, Grinnell to the contrary (8), despite the definitely greater incidence of lymph node involvement in surgical specimens from the right colon.

Wide resection for cancer of the colon has been advanced because of such reports as that of Gilchrist and David in 1948. Autopsy was performed in 11 patients dying in the postoperative period, 4 bodies containing retroperitoneal metastases, in 3 of which 1.5 centimeters wider dissection would have apparently encompassed the lymphatic extensions. Another report is that of Rosi, in which 36 cases of carcinoma of the left colon were presented: 14 per cent had positive nodes within 2 centimeters of the origin of the inferior mesenteric artery.

The enormous importance of articles such as those just cited led to a succession of related reports urging more extensive lymphatic resections, especially in carcinomas of the flexures, transverse colon, left colon, and rectum, the schema of Rosi appearing particularly worthy of emphasis. All of the authors' patterns of resection are based on wide resection of the intestine coupled with extensive resection of the vascular supply. Virtually all of these outlines of vascular pattern follow the stereotyped pattern of colic branches off the superior mesenteric artery, which we have found to exist in but 23.8 per cent of cases. In view of the marked variability of the colic vascular pattern, it would seem indicated to explore atraumatically, but carefully the individual pattern of each patient upon whom cancer surgery is undertaken.

What steps can be taken to improve our results in surgery for colic cancer? At the outset, it should be stated that statistical proof has not yet accumulated to support the adoption of wider resection and of attempted quarantine of the gross tumor. However, the vast amount of careful study of lymphatic metastasis, of venous spread, of intraluminal and extraluminal cancer emboli, of intramural extension, and of multiple primary tumors, all lead one to accept, until proved otherwise statistically, the precepts about to be discussed.

First, as mentioned, the arterial pattern should be ascertained, the goal being to transect at its origin the arteries supplying a given cancer zone. Any thought given to blood supply for the subsequent anastomosis should wait until an honest cancer resection has been accomplished. Generally poor results in cancer of the transverse colon and hepatic and splenic flexures may not only be related to tumor manipulation through inadequate incisions, but unwarranted compromise with the scope of resection.

The authors should like to emphasize that the extent of resection should not be determined upon the basis of a textbook conception of vascular pattern present in the particular patient at surgery. The following general precepts are recommended: (1) Ligate at its origins from the superior mesenteric artery or the aorta the arterial supply on either side of a tumor, unless that tumor lies in the proximal transverse colon. In this case middle and left colic arteries

should be ligated. (2) Ligate at their origins both the middle colic and inferior mesenteric arteries in tumors of the distal transverse colon and splenic flexure. (3) Perform inferior mesenteric artery ligation for tumors of the left colon and rectum. (4) If a common stem origin exists for 2 major colic arteries, ligate at the superior mesenteric origin of the common trunk.

Venous return from a cancer of the colon should be interrupted before mobilization of the tumor segment. In the right colon, this will be done simultaneously with arterial and lymphatic ligation, because the veins parallel the arteries. The first operative approach in right colon lesions is directed, then, at the vascular roots of the right colon. In cancer of the left colon and rectum the approach is again medial, inferior mesenteric artery being ligated at its aortic origin while the inferior mesenteric vein is ligated at its entrance near the splenic or inferior mesenteric vein. The marginal or paracolic vessels should be ligated at some distance on either side of the tumor. These ligatures should be separate and distinct from the umbilical tape ties of the colon itself, which may not be snug enough to prevent venous embolization along the marginal veins. Amplifying an earlier report (6), Turnbull (25) stated that in 33 patients with carcinoma of the colon upon whom the venous return was first isolated, the venous blood revealed tumor cells in 10 of these cases following massage of the tumor. In the next 67 cases in which tumor was not handled unduly, 10 further cases presented positive cells in the venous return.

Ties of umbilical tape should be placed securely at points both proximal and distal to the tumor, these points being preferably 30 centimeters from the cancer. Later in the operation, following resection of the segment of involved mesentery and colon, saline or aqueous zephiran irrigation of the bowel proximal and distal to the quarantined cancer segment should be performed prior to anastomosis. This act is of particular importance in anterior resection in which the segment distal to the tumor may be but one-third the optimal length. The steps of bowel ligation and of irrigation of remaining segments are taken because Cole and other authors have substantial evidence to present, indicating that free cancer cells within the bowel lumen are often incorporated into the suture line, causing later recurrence at the anastomosis. There is a direct relationship between the incidence of positive cancer smears from the mucosal surface and the distance from the tumor at which the smears are taken: whereas 82 per cent were positive if taken in specimens 5 centimeters from the tumor, only 10 per cent of smears were positive if taken 30 centimeters from the cancer.

A generous resection of colon will more than adequately encompass intramural spread of carcinoma, Grinnell (9) finding that a margin of 5 centimeters was adequate in his specimens to remove all apparent spread in the lymphatics of the subserosa and of the perirectal fat. Others caution that postoperative shrinkage may give a misleading index of safety, and therefore insist on a margin of 12 to 15 centimeters of grossly normal bowel before attempting an anterior resection. Furthermore, it must be remembered that the external impression of the confines of a cancer are often several centimeters short of its actual gross dimensions when the specimen is opened.

With a minimum of handling, tumors of the colon should be wrapped with an apron of polyethylene sheeting, the sheeting then firmly secured with ties about the tumor. In a series of 20 cases of colic cancer in which smears were made from the serosal surface overlying the tumor, cancer cells were identified in 2 cases. The possibility of peritoneal studding is certainly present, and precautionary measures seem warranted.

Endoscopic examination of the nonresected colon is indicated in view of the high incidence of polyps and cancer to be found in the residual bowel. Mayo and Schlicke (15), in 131 autopsies on patients dying soon following surgery for carcinoma of the colon and rectum, found 37.4 per cent had polyps

in the remaining colon and 5.3 per cent had a second carcinoma.

In summation, the principal tenets, drawn from the collective experience in cancer surgery of the past decade, are the following: (1) adequate operative exposure, with greater utilization of long transverse and oblique incisions, thus minimizing subsequent trauma in mobilizing the tumor; (2) an initial approach aimed at the vascular roots of the colon segment involved, immediately ascertaining and ligating its arterial, lymphatic, and venous components; (3) ligation of the marginal artery and vein at a distance on either side of the cancer segment; (4) ligation of the colon, preferably 30 centimeters on either side of the lesion; (5) effective envelopment of the tumor in an impervious cover; (6) resection of the segment demarcated by these steps; (7) irrigation of the remaining proximal and distal segments of colon; (8) coloscopy through the proximal and distal stomas, with appropriate attention to polyps or further carcinoma; and (9) consideration, finally, to effecting an anastomosis.

The steps listed make decided demands on the surgeon and upon operating time. However, as Ravdin said recently: "Surgeons must search themselves that the motives which lead them to do lesser operations for a disease (cancer of the colon and rectum) which will kill 54,000 or more of our people this year, are not conditioned by an initial lower mortality, or an immediately grateful patient."

Surgical considerations of the middle colic artery are highly significant in upper abdominal surgery. Although we did not find a case in our series, several instances of middle colic artery origin from the celiac axis have been reported, the possibility of its injury being evident in surgery in and about the duodenal loop. Although the middle colic artery usually lies somewhat lateral to the area of duodenal mobilization in gastrectomy, it has occasionally been tied, and led to death.

Our series revealed an 8.6 per cent incidence of accessory middle colic arteries, one of which often passes across the usually avascular portion of the transverse mesocolon. Complications may be avoided in performing retrocolic gastroenterostomy if the occasional presence of this vessel is remembered.

The absence of the middle colic artery (3.6 per cent of our series) emphasizes in the occasional case the signal importance of the marginal artery: it must necessarily span an extended length of colon. The integrity of the marginal artery should be preserved in performing a transverse loop colostomy, the restraining rod passing between colon and marginal artery. This note of caution would be of particular importance in the cases in which the marginal artery is absent or of inconsequential caliber near the splenic flexure.

SUMMARY

The authors have presented a study from 600 cadavers concerning the patterns of colic arteries originating from the superior mesenteric artery. It has been stressed that the patterns represent, not anomalies, but the normal and expected variations of blood supply to the right colon.

Twenty-four patterns were found, 3 of which comprised 68 per cent of the series, these 3 patterns differing only in the specific origins of their constituent colic arteries, but were alike in possessing but a single artery to each of 3 areas of the colon: ileocolic, ascending, and transverse.

Although the ileocolic artery was present in all specimens, the right colic was absent in 12.6 per cent, the middle colic absent in 3.6 per cent of our series.

The ileocolic artery was always single, whereas right colic arteries were multiple in 9.4 per cent, middle colic arteries multiple in 8.6 per cent of cases.

The left colic arteries was found to have an anomalous origin from the superior mesenteric artery system in 2 cases. The ileocolic, right colic, and middle colic arteries were found to originate in every case

either directly or by a common stem with another vessel from the superior mesenteric artery. No case of middle colic artery originating from the celiac axis system was found, though references for such occurrences were cited.

From smaller series were noted measurements on the following: (1) lengths of colic arteries, (2) sites of origin of colic arteries on the superior mesenteric artery, (3) site of primary bifurcation of the middle colic artery, and (4) lengths of the several colic segments.

The marginal artery was defined and discussed, and it was noted that failure of continuity seemed most likely between the ileocolic and right colic arteries, and between the middle and left colic arteries near the splenic flexure.

Several observations were made on the terminal arteries, namely their tendency to branch once or twice in passing from the marginal artery to bowel wall, and the slightly increased number of vessels entering the right as compared to the left colon.

It is emphasized that the current concept of radical surgery for cancer of the colon rests upon wide lymphatic extirpation. Since lymphatic structures follow the arteries of a supply to a cancer segment, a vascular resection should be based, not on the textbook pattern, but on the basis of an expected variant pattern of colic arteries discussed in this article.

An outline of resection for cancer of the colon is presented, utilizing not only a knowledge of resection based on expected arterial variants, but on the following principles of tumor quarantine prior to mobilization of the involved colon: ligation of the colic arteriolymphatic and venous structures bounding a cancer segment, the operative approach being midline at the vascular roots of the colon; ligation of paracolic marginal vessels and ligation of the colon itself, preferably 30 centimeters on either side of the tumor; envelopment of the tumor in an impervious cover with minimal handling; mobilization and resection of the demarcated specimen; irrigation of the remaining proximal and distal segments of colon; coloscopy; and, finally, anastomosis.

The danger of the occasional middle colic artery originating from the celiac axis system, the vulnerability of the marginal artery with absence of the middle colic artery, the occasional diminution in size of the marginal artery near the splenic flexure, and the not infrequent left mesocolic course of a middle colic artery are all discussed.

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PERIPHERAL ARTERIAL EMBOLI

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EMBOLECTOMY is one of the simpler and older established procedures in the field of arterial surgery. Sabanieyeff in 1895 attempted to remove an arterial embolus, but it was not until 1911 that Labey performed the first successful embolectomy. Since that time reports of many other experiences and reviews of the literature on the subject have appeared. The majority of reports, however, have dealt only with small numbers of patients treated by the authors.

It is the purpose of this report to review the literature, analyze a series of local patients, and to comment upon those factors which, in our experience, determine the success of the treatment and also the variable factors which contributed to a poor result. The authors' own study is based on a series of 64 patients who had a total of 86 peripheral arterial emboli. These patients were treated at Emory University Hospital, the Grady Memorial Hospital, and the Atlanta Veterans Administration Hospital during a 10 year period (1946 to 1956). Forty of the patients were males and 24 were females. The peak incidence was encountered in patients in the sixth and seventh decades of life (Table I). The youngest patient was 13 years of age and the oldest, 87.

ETIOLOGY

Embolism occurs when a clot or bit of foreign material, transported by the blood stream to a segment of the vascular bed, is brought to a halt because of its size or consistency, and thus causes obstruction. Emboli may be solid, liquid, or gaseous. They may be composed of foreign materials, bacterial vegetations, or even tumor cell masses. However, unless otherwise specified, the term is generally understood to be a portion of blood clot derived from a parent thrombus located elsewhere. In this discussion, only peripheral arterial emboli will be considered.

Arterial emboli may stem from several sources; however, the majority originate in a diseased left side of the heart. Haimovici found this to be the case in 96 per cent of the 330 patients he studied. In Bull's report, the origins are defined as: (1) left side of heart, for (a) mural thrombi secondary to arrhythmia, myocardial infarction, trauma (from surgery), mitral stenosis with endocardial pockets, failing heart from any cause, (b) vegetation on valves, (c) foreign bodies, (d) tumor; (2) large arteries (aorta), for (a) sclerotic plaque, (b) trauma (blunt, surgical or other followed by thrombosis), (c) aneurysms, (d) foreign bodies; (3) pulmonary veins, for (a) thrombosis, (b) trauma followed by thrombosis, (c) tumor; (4) right side of heart (septal defect) for mural thrombi; (5) systemic veins (septal defect), for thrombosis. The sources of the authors' 86 emboli are shown in Table II.

Mural thrombi, formed on the left side of the heart, account for most of the peripheral arterial emboli. Rheumatic heart disease and heart disease following myocardial infarction are the most common causes. A mural thrombus forms within the lumen of the left side of the heart during arrhythmia or following injury to the heart wall, and then dislodges to settle elsewhere as an embolus. Frequently, the patient's history shows that changes have been made recently in his medical treatment, or that there has been an alteration in his pulse rate or heart rhythm.

Although mural thrombi are produced by many disorders of the heart, those resulting

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TABLE I.—AGE INCIDENCE

Age, years	*No. of patients*	*Per cent*
10–19	1	1.5
20–29	0	0
30–39	6	9.4
40–49	11	17.2
50–59	13	20.3
60–69	16	25.0
70–79	11	17.2
80–89	6	9.4
Total	64	

TABLE II.—SOURCES OF 86 PERIPHERAL ARTERIAL EMBOLI IN 64 PATIENTS

	No. of emboli	*Per cent*
Auricular fibrillation	43	50.0
Myocardial infarction	27	31.4
Subacute bacterial endocarditis	4	4.7
Sclerotic aortic plague	3	3.5
Foreign body (.32 bullet)	1	1.2
Undetermined	8	9.3

TABLE III.—SITES OF EMBOLI

	No.	*Per cent*
Femoral	36	41.9
Popliteal	15	17.4
Brachial	14	16.3
Iliac	13	15.1
Aorta	5	5.8
Radial	2	2.3
Tibial (posterior)	1	1.2
Total	86	

from auricular fibrillation due to rheumatic heart disease or from arteriosclerotic heart disease are most often responsible for subsequent peripheral arterial emboli. In patients with rheumatic heart disease, the mural thrombi are located predominantly in the auricular appendage or on the wall of the auricle, whereas those that follow myocardial infarction occur predominantly in the ventricle. Jordan and associates found that about 50 per cent of the intracardiac mural thrombi in patients with mitral stenosis and auricular fibrillation occurred in the auricular appendage and 50 per cent on the remaining atrial wall. Because thrombi also occurred in a few patients with normal rhythm, these authors concluded that endocardial pockets, so often found in the left atrial wall in mitral stenosis, may also be a site of origin.

In patients with active rheumatic heart disease and subacute bacterial endocarditis, emboli may originate from vegetation on the heart valves. However, these emboli, which may be multiple and small, usually cause visceral disturbance rather than obstruction of a larger peripheral vessel.

Myocardial infarction is the second most frequent cause of mural thrombi. Garvin found mural thrombi in 67 per cent of the patients with coronary thrombosis and myocardial infarction that he studied at autopsy. In approximately 90 per cent of these cases, the thrombi were located within the ventricles, especially the left ventricle. Schlichter and associates found ventricular aneurysms in 20 per cent of all cases of myocardial infarction seen by them at postmortem and 51 per cent of these aneurysms were associated with thromboembolism. They observed that 70 per cent of the patients with aneurysms had had inadequate bedrest at the time of infarction. This observation supports the opinion of Lary and de Takats that early ambulation following myocardial infarction may increase the incidence of arterial emboli. In Haimovici's series, 31.5 per cent of the systemic arterial emboli followed myocardial infarction.

Other disorders of the heart may also play a role in the development of arterial emboli. For example, marked dilatation of the left side of the heart predisposes formation of mural thrombi, from which arterial emboli may arise. In rare instances, a tumor embolus has occurred in the left side of the heart. Undoubtedly, it is safe to predict that as more open and closed cardiac surgery is performed, mural thrombi resulting from the procedures will account for an increasing number of arterial emboli.

Sources of arterial emboli other than the heart are rare, but worth considering. They may originate in the pulmonary veins as a result of thrombosis, trauma, or tumor. Arteriosclerotic plaques detached from the wall of the aorta constitute the most frequent source of emboli originating in the great vessels. Thrombi may occur in the large vessels following surgery (aortic graft) or trauma, become detached, and be carried to the peripheral vessels. Occasionally,

TABLE IV.—SITES OF EMBOLI—REVIEW OF LITERATURE

Author	*Total No. of cases*	*Upper extremity*	*Aortic*	*Iliac*	*Femoral*	*Popliteal*
Lovingood	6	—	4	—	2	—
Dye	65	14	5	7	23	16
Haimovici	312	53	30	55	127	47
Veal and Dugan	28	13	3	3	5	4
Proffitt	13	—	1	5	7	—
Richards	56	11	12	3	25	5
Flasher	212	—	23	20	123	46
Daley	133	39	23	21	29	21
Des Prez	82	11	11	10	27	23
Andrus	71	13	10	5	20	23
Warren and Linton	232	59	30	30	80	33
Danzis	127	29	11	23	52	12
Key	380	46	17	66	208	43
Hopkins	45	13	7	2	18	5
Pearse	279	46	31	48	126	28
Iselin	9	2	0	5	2	0
Massell	14	—	1	3	5	5
Austin	24	3	0	2	10	9
No. of cases	2,088	352 (17)	219 (11)	308 (15)	889 (42)	320 (15)
McGarity, *et al.*	86	16 (19)	5 (6)	13 (15)	36 (42)	16 (18)

The figures in parentheses indicate percentages.

foreign bodies may lodge in the left side of the heart or in a large vessel and act as emboli. This happened to 1 of our patients, shot with a .32 caliber pistol. The bullet entered a major vessel in the chest and stopped at the bifurcation of the left femoral artery. When the bullet was removed, normal circulation was restored in the affected extremity.

Paradoxic emboli are those that originate in the venous system and reach the arterial tree by passing through an interventricular septal defect or patent foramen ovali. Clots may come from various sites of thrombosis in the peripheral venous system or from mural thrombi within the right side of the heart. Several cases of paradoxic emboli have been reported.

SITES AND NUMBER OF EMBOLI

Over 40 per cent of the 86 emboli in the authors' series occurred in the femoral vessel (Table III). Vessels of the upper extremities accounted for 18.6 per cent. These percentages are in close agreement with those derived from a review of 2,088 peripheral arterial emboli reported in the literature (Table IV).

Any embolus may be one of a series or one of several occurring simultaneously. In a case reported by Alergant, an embolus occurred in a major vessel in each of the 4 extremities simultaneously. One of our patients had 5 peripheral emboli, all occurring at different times.

In our series, 16 patients (25 per cent) accounted for 38 (44 per cent) of the peripheral emboli: 1 patient had 5 emboli, 3 patients had 3, and 12 patients each had 2. As with single emboli, auricular fibrillation and myocardial infarction were responsible for the majority of these multiple emboli: auricular fibrillation in 10 patients (62.5 per cent), myocardial infarction in 4 patients (25 per cent), and undetermined source in 2 patients (12.5 per cent).

PATHOPHYSIOLOGY

The site of obstruction, spasm of the major vessel and its collaterals, and distal and proximal thrombosis determine whether the blood supply to the extremity will be adequate.

Emboli usually stop at a bifurcation of a vessel, although they may occasionally lodge in a straight segment. Obviously, if the obstruction occurs at a point where numerous branches act as collaterals, the prognosis is much better than otherwise.

The etiology of spasm associated with embolus is not clearly understood, but several factors may be considered. A continued

hammering effect of the systolic pressure in the vessel tends to impact the mass and complete the obstruction. The mild proximal dilatation and local irritation of the vessel which result may influence the production of spasm both in the major vessel and in its collaterals by a direct or reflex mechanism. Sudden distention of an artery can cause arterial spasm, and pain may also be a contributing factor. Spasm may be relieved by paravertebral blocks or sympathectomy, or occasionally by application of papaverine directly on the vessel.

The occurrence of distal or proximal thrombosis, or both, is almost inevitable if anticoagulants are not given, but its extent is unpredictable. We made an effort to correlate the amount of progressive thrombosis with the length of time between the occurrence of the obstruction and the beginning of treatment, but could find no consistent relationship. Distal thrombosis tends to be extensive; proximal thrombosis is limited, unless circulation is failing. Recently, one of us (24) demonstrated the presence of a static column of blood proximal to the obstruction. The current, or flow, of blood prevents the extension of the proximal thrombus beyond the first major collateral.

Other factors influencing the degree of thrombosis include the amount of vasospasm present, the increase in the clotting tendency, and the status of the collateral circulation. Progressive thrombosis, by occluding the orifices of important collaterals or by extending into their lumina, may endanger the circulation to the limb. Thus when an embolus occurs, the mechanical obstruction of a major vessel, arterial spasm of the affected vessel and collaterals, and the development of distal and proximal thrombosis present problems which must be resolved.

CLINICAL MANIFESTATIONS

Pain or paresthesia at the site of the lesion or distal to it constitutes the most frequent initial symptom of arterial embolus. If the patient is conscious and unsedated at the time the embolus occurs, he may localize the pain and describe it as a sharp, burning or stinging discomfort. The patient's perception of the initial pain is clinically significant, for the site of his discomfort often proves to be the point at which the embolus has stopped. However, there may be no pain if the obstruction is incomplete or if a vessel such as the aorta, which is unable to contract, is involved. As has been shown by Leriche, an area of arterial thrombosis leads not only to local arterial spasm but also to generalized arterial spasm in the collateral circulation of the extremity. This spasm, initially manifested by symptoms in the area of occlusion only, is followed by pain due to ischemia in the tissues distal to that point. A propagating thrombus may develop either proximally or distally to the embolus; when vasospasm is added to the picture, clinical examination may fail to disclose pulsation even in the proximal arteries, and the actual site of the embolus may be obscured. The sudden, sharp pain designating arrival of the embolus at a certain point in the arterial tree is to be differentiated from the ischemic, neuritic pain resulting from prolonged arterial insufficiency.

Distal pain depends upon many factors: vasomotor responses; degree of collateral circulation; completeness and permanence of the blockage, as well as its site; and preexisting arterial disease. Other factors will also influence the time of onset and severity of distal pain. It will develop more slowly in the inactive, paralyzed, or bedridden patient. It is more prevalent and severe in the muscular portion of the extremity that requires the greatest amount of blood. The more rapid the onset and progression of ischemia, the more rapid will be the progression of the distal pain.

One young individual, who was observed by the authors 24 hours after an embolus lodged in the terminal aorta, complained only of slight paresthesias in his feet upon walking. An embolectomy was performed with good results more than 24 hours after the onset of symptoms. Haimovici found that 82 per cent of his patients had sudden

onset of pain and 12 per cent had slowly progressive discomfort. Richards reported that 37 (70.5 per cent) of his 48 patients experienced sudden onset of pain.

In most individuals, particularly when pain is an initial symptom, color and temperature changes are noticeable very soon after arterial occlusion develops. The distal extremity first becomes pale and then marbleized in appearance. It becomes cold, and often a definite line of demarcation or temperature difference can be established. Generalized cyanosis develops, and if sufficient time elapses before treatment, early mummification of the extremity will be evident. These findings sometimes develop within a very short period of time.

No pulses can be palpated distal to the site of complete arterial obstruction. Lack of pulsation, however, may be deceptive if vasoconstriction is generalized. For example, a patient with an embolus to the popliteal artery may have such severe vasoconstriction that no pulse can be felt in the femoral artery. The use of a sensitive oscillometer is sometimes helpful in determining the site of the obstruction, but the results may be erroneous.

When the arterial flow into the extremity is insufficient, the venous bed collapses. As ischemia progresses, symptoms of paresthesia, pain, and weakness leading to paralysis are to be expected. Since sensation returns to the affected extremity so rapidly when the arterial obstruction is relieved early, the authors believe that nerve ischemia rather than permanent nerve damage is responsible for the anesthesia. If circulation is restored before true tissue damage develops, complete restoration of function is to be expected. If irreversible damage has occurred, fibrosis and a picture of ischemic contracture will develop even though arterial pulses are completely restored.

Differential diagnosis. It is not always easy to diagnose arterial embolism; frequently, the diagnosis involves a process of elimination. Careful consideration must first be given to any potential source of an embolus. The possibility of arterial embolism exists whenever arterial occlusion develops suddenly. Arterial thrombosis secondary to arterial disease, arterial spasm, thrombosis due to injury, and severe vasospastic phenomena associated with other conditions such as thrombophlebitis (phlegmasia cerulea dolens) may account for the arterial insufficiency. It is most difficult to differentiate between an arterial embolism and thrombosis at the site of an atheromatous plaque. The latter condition may be induced suddenly by abnormal posture, trauma, or other factors, and the resultant ischemia may closely simulate that of arterial embolism. As a rule, however, the onset is more gradual and the history sufficiently distinctive to permit correct diagnosis. Ischemic symptoms and even intermittent claudication develop only as the result of severe arterial occlusion.

Arterial spasm is also associated with fractures or other injuries that occur in the vicinity of blood vessels.

Occlusions of the popliteal vessel are more commonly due to thrombosis than to embolism.

TREATMENT

It is generally agreed that the treatment of arterial embolus is a medical emergency. The ultimate outcome depends largely upon early recognition and expedient treatment of this condition. When the onset of symptoms is dramatic, the patient usually loses little time in seeking help. Delay in therapy is more commonly encountered in individuals whose symptoms are less conspicuous, either because their collateral circulation is good, or because the occlusion is less extensive. However, in these individuals adequate or borderline circulation to an extremity may become seriously impaired within a very short time if a thrombus propagates either distally or proximally from the site of the embolus. The development of sequelae is directly related to propagation of the thrombus or tissue death due to ischemia. Hence, treatment should be started as soon

as possible—preferably within 6 to 12 hours after the embolism occurs.

Not every patient with an arterial embolus is a candidate for embolectomy. Each patient must be individually studied and equal consideration must be given for operative and nonoperative intervention before a choice can be made. Among the factors to consider in selecting the proper treatment for the individual patient are his general condition, the coexistence of heart disease, and the adequacy of the collateral circulation in the affected extremity. The site of occlusion also furnishes some indication as to what form the treatment should take. Some patients with an embolus in the popliteal vessel or in the upper extremity can be satisfactorily managed with conservative measures; others require prompt surgical removal of the embolus. When conservatively treated patients with emboli at these sites fail to show improvement, surgery is indicated. Gangrene can develop from emboli in these locations, as elsewhere. An embolus involving the aorta, or iliac or femoral artery should be treated as a surgical emergency. This is particularly true of the embolus that lodges at the bifurcation of the aorta; if surgical removal is unfeasible, the patient may lose his limbs—if not life itself.

Conservative treatment is indicated (1) for patients so critically ill from other diseases or from simultaneous cerebral or visceral embolism that any but supportive treatment may be hazardous, and (2) for patients with adequate collateral circulation in the affected extremity. In these patients, sympathetic blocks should be administered immediately to relieve the reflex spasm of the collateral vessels. If repeated blocks are necessary, a polyethylene tube may be inserted and left in the area of the sympathetic chain for future use, since the use of blocks are contraindicated after a therapeutic level of anticoagulants has been obtained. Anticoagulant therapy is imperative to prevent propagation of thrombi and to insure the patency of collaterals; therefore, aqueous heparin and dicumarol are given early and the use of heparin is discontinued after 48 to 72 hours. Other adjuncts include the oscillating bed and vasodilator drugs. Systemic vasodilator drugs are not recommended as a rule, because generalized vasodilatation tends to decrease the blood flow to the affected extremity. However, papaverine administered intravenously in dosages of 1 grain every 6 hours may prove to be of value.

In the surgically treated group, any of the following 5 procedures may be used as indicated: (1) Embolectomy, as the preferable procedure, should be performed when possible. (2) Arteriectomy may be necessary if local conditions make closure of the arteriotomy impossible. In this procedure, the local stimulus for vasospasm is removed and the incidence of propagating clots is reduced; in addition, periarterial sympathectomy is accomplished, which may lead to increased distal blood flow. Whenever possible, continuity of the vessel should be restored by end-to-end anastomosis or by bridging the defect with an arterial or other type of graft. (3) Permanent interruption of sympathetic pathways, rather than embolectomy, may be indicated when smaller arteries are involved. As a primary therapeutic trial, paravertebral blocks should precede this procedure. (4) Amputation becomes necessary if gangrene is present. (5) Resection of the left auricular appendage and mitral commisurotomy have been advised in a few selected patients to prevent recurrent emboli.

The time interval between the onset of the embolus and the operation is important. Although emboli have been removed successfully several hours or even days after their occurrency in some patients, successful outcome of the procedure depends upon the existence of an undisturbed collateral circulation that is adequate to provide basal nutrition to the affected part. Failure of arterial embolectomy has often been attributed to the amount of time permitted to elapse between the occurrence of the embolus and performance of an embolectomy.

Various authors have tried to establish optimum time intervals. Heanley considers the first 10 hours most auspicious. Pearse, in reviewing 282 embolectomies, found little difference in results of operations performed within the first 5 hours and in those performed during the second 5 hour period. Even if the patient is not seen until later and circulation is inadequate but damage does not appear to be irreversible, an embolectomy should be attempted. Mortality following embolectomies is not usually due to the surgical procedure but rather the result of gangrene or associated diseases, except when the embolus is at the bifurcation of the aorta or iliac vessels.

When embolectomy is required, a preoperative sympathetic block is occasionally indicated, although in some instances this may cause the embolus to become dislodged, slip further down the arterial tree, and become more difficult to find at surgery. It is wise to give aqueous heparin intravenously at the time of diagnosis or after the sympathetic block in order to prevent additional thrombosis proximal and distal to the embolus. The effect of the heparin is usually gone by the time the operation is performed; therefore, there is no excessive amount of bleeding.

Usually, embolectomy is performed with local anesthesia. However, when the embolus is lodged at an aortic or iliac bifurcation, spinal or general anesthesia is necessary. It is not difficult to explore a peripheral vessel under local anesthesia, and this should be done when circulation to the extremity is questionable. The vessel is isolated distal to the embolus and a soft rubber tourniquet or Pott's clamp is applied to prevent the embolus from sliding distally. Then the proximal vessel is dissected free and controlled. Usually a small incision just above the bifurcation will permit removal of the obstruction. After the embolus has been removed, the patency of the vessel is tested by demonstrating a good proximal and retrograde blood flow. If there are proximal and distal thrombi, the clots can sometimes be removed by milking them out through the original incision, although it may be necessary to remove additional ones through multiple small incisions in the affected vessel. Occasionally, a retrograde irrigation of the vessel is required. In the lower extremity this is done by isolating the posterior tibial artery at the ankle, inserting a cannula or polyethylene tube upward and forcefully irrigating the vessel with a heparin solution. If this proves inadequate, a long polyethylene tube or ureteral catheter may be inserted to help dislodge the clots. During the process, the exposed lumens are kept irrigated with a heparin solution to prevent local thrombosis. After the vessel is clear, the arteriotomy is closed with a continuous suture of arterial silk.

Arteriography is often helpful in determining whether all clots have been extracted. If a segment of arteriosclerotic narrowing is associated with the embolus, an arterial graft may be needed to restore the efficiency of the vessel. Thrombo-endarterectomy may also sometimes prove to be a useful procedure.

The direct approach to the embolus is usually preferable. However, if the embolus has lodged in the popliteal vessel, it may be best to approach it indirectly by opening the superficial femoral artery in the distal portion of Scarpa's triangle and milking the embolus upward to this opening, or by using retrograde irrigation through the posterior tibial artery. The indirect approach may be the more successful one, because the popliteal vessel is small and the incidence of postoperative thrombosis at this site is high. Furthermore, the interruption of collateral circulation by surgery in the area of the popliteal artery may be sufficient to embarrass the extremity still further and lead to gangrene.

It is not usually necessary to administer aqueous heparin immediately after the operation if an adequate flow of blood has been obtained. However, it is advisable to use long acting anticoagulants (dicumarol) for several days or months in order to help pre-

TABLE V.—RESULTS OF EMBOLECTOMIES—REVIEWED IN LITERATURE

Author	*Total No. of cases*	*Upper extremity*	*Aortic*	*Iliac*	*Femoral*	*Popliteal*
Lovingood and Patton	6	—	4	—	2	—
Dye	65	14	5	7	23	16
Klingensmith	19	—	—	9	10	—
Wallace	2	—	—	—	2	—
Proffitt	13	—	1	5	7	—
Richards	12	—	—	2	10	—
Haimovici	29	6	2	2	19	—
Flasher	40	—	3	8	25	4
Danzis	124	29	11	22	51	11
Key	36	4	6	—	21	5
Pearse	278	46	31	48	126	27
Nystrom after Harbin	379	45	17	66	208	43
Iselin	4	1	—	1	2	—
Massell	9	—	1	3	5	—
Daley	15	7	—	—	8	—
Des Prez	25	4	1	7	13	—
Andrus	2	—	2	—	—	—
Fiddian	2	2	—	—	—	—
Eddy	2	—	—	—	2	—
Scott	3	—	—	—	2	1
Veal and Dugan	16	3	3	3	5	2
Warren and Linton	78	17	14	15	32	—
Austin	6	—	—	—	5	1
No. of cases	1,167	178 (15)	101 (9)	198 (17)	580 (50)	110 (9)
Successful	444 (38)	111 (62)	30 (30)	60 (30)	205 (35)	38 (34)
Unsuccessful	723 (62)	67 (38)	71 (70)	138 (70)	375 (65)	72 (66)

The figures in parentheses indicate percentages.

vent recurrence of emboli. Since anticoagulants have been added to the armamentarium for myocardial infarction, we have noticed a decrease in the incidence of emboli. Postoperative sympathetic blocks are sometimes necessary to decrease or prevent reflex spasm. These may be repeated if they prove beneficial and discontinued when an adequate level of anticoagulization is obtained. During the first few postoperative days, the oscillating bed may be used to increase circulation. Vasodilator drugs such as papaverine hydrochloride may also be indicated.

RESULTS

The outcome was reported as successful in only 444 (38 per cent) of the 1,167 embolectomies for which results were given in the literature (Table V). The best results were obtained in the upper extremity and next in the femoral artery. In the smaller series reported by the authors, pulsation or adequate circulation was restored in the affected extremities following 36 (71 per cent) of the 50 embolectomies (Table VI), and in 17 (47 per cent) of the 36 patients who were treated by conservative measures (Table VII).

Femoral. Thirty-six emboli stopped at the bifurcation of the common femoral artery. In 26 instances the patients were treated by embolectomy, and only 4 of them required subsequent amputation. The remaining 10 were treated by the conservative method; ultimately 7 amputations were performed. Seven of the 36 patients in this group died from associated diseases.

Popliteal. There were 15 cases of popliteal emboli with 3 deaths from associated diseases. Results of operative and nonoperative treatment were much the same in this group.

Iliac. Thirteen emboli occurred in the iliac vessels. Three of the 5 embolectomies were successful, but 7 of the 8 conservatively treated patients required amputation. Five of the 13 patients died from associated diseases.

Aortic. Five patients had a saddle embolus of the aorta. Embolectomies were performed in 4 of these patients, but only 1 was successful. The fifth patient's condition precluded an operation and this patient died

within a few hours from associated diseases.

Brachial. Fourteen emboli occurred in the brachial artery. Eight patients were treated by embolectomy with good results, and 6 were treated by nonoperative methods with return of adequate circulation. There were no deaths in this group.

The return of circulation, and the morbidity and mortality depend on many factors: the site of the embolus, age of the patient, time interval between onset and treatment, associated diseases, state of collateral circulation, multiplicity of emboli and postoperative thrombosis. The location of the embolus particularly is a major factor in the final results.

Although the results of successful embolectomies are dramatic, unsuccessful operations are followed by death, loss of limb, or varying degrees of functional impairment in the extremity.

Mortality. In our series of 64 patients, the mortality rate was 29.6 per cent. Twelve (18.7 per cent) of the 50 patients who had embolectomies and 7 (10.9 per cent) of the ones treated conservatively died. Although the embolisms contributed to the mortality rate, the majority of deaths were due to associated diseases (Table VIII). Surgery was not usually a major factor in the deaths. Local anesthesia was used in most of the surgical procedures, except when the aorta or the iliac vessel was involved. No information is available on follow-ups of these patients after they left the hospital. However, according to Strombeck the average life expectancy after embolectomy is only a few years, with the majority of deaths due to heart disease or cerebral embolism. Embolectomy appears to be the treatment of choice for emboli of the aorta and iliac and femoral vessels, provided the patient's condition permits carrying out this procedure. For emboli of the vessels of the upper extremity and of the popliteal vessels, the type of treatment to follow depends upon the status of the collateral circulation, the presence of spasm, and also upon the resulting thrombosis.

TABLE VI.—RESULTS OF EMBOLECTOMIES

Site	*Total*	*Pulses returned*	*Adequate circulation*	*Limited function*	*Amputation*	*Deaths**
Femoral	26	9	12	1	4	5
Popliteal	7	1	2	0	4	3
Iliac	5	2	1	0	2	1
Aorta	4	1	0	0	3	3
Brachial	8	6	2	0	0	0
Total	50	19	17	1	13	12
		Successful—71%		Unsuccessful—29%		

*The majority of deaths were due to associated diseases.

TABLE VII.—RESULTS FROM NONOPERATIVE TREATMENT

Site	*Total*	*Pulses returned*	*Adequate circulation*	*Limited function*	*Amputation*	*Deaths*
Femoral	10	1	1	1	7	2
Popliteal	8	1	4	0	3	0
Iliac	8	0	1	0	7	4
Aorta	1	0	0	0	1	1
Brachial	6	5	1	0	0	0
Radial	2	0	2	0	0	0
Posttibial	1	0	1	0	0	0
Total	36	7	10	1	18	7
		Successful—47%		Unsuccessful—53%		

TABLE VIII.—CAUSE OF DEATH IN 64 PATIENTS*

	Embolectomy	*Nonoperative*	*Total*	*Average age, years*
Congestive heart failure	7	1	8	65
Myocardial infarction	1	1	2	76
Subacute bacterial endocarditis	1	0	1	13
Cardiac arrest	1	0	1	69
Multiple visceral emboli	1	3	4	66
Cerebral thrombosis	0	1	1	79
Novocain reaction	0	1	1	75
Undetermined	1	0	1	74
Total	12	7	19	
(Per cent)	(18.7)	(10.9)	(29.6)	

*Within 3 weeks following emboli.

SUMMARY

1. Sixty-four patients were treated for a total of 86 peripheral arterial emboli. One-fourth of them had 2 or more peripheral emboli.

2. The most frequent source of arterial emboli was a mural thrombosis in the left side of the heart in patients with auricular fibrillation or recent myocardial infarction.

3. The most frequent site of occurrence was at the bifurcation of the common femoral artery.

4. The best results were obtained when treatment was started within the first 6 to 12 hours following occurrence of the embolus.

5. Seventy per cent of the embolectomies in the series presented by the authors were

successful as compared to 38 per cent of the 1,167 embolectomies for which results were given in the reviewed literature.

6. The mortality rate in the 64 patients was 29.6 per cent (18.7 per cent in the surgically treated group and 10.9 per cent in the conservatively treated group). Most of the deaths were due to associated diseases.

7. When an embolus lodges in the popliteal vessel or in an artery of the upper extremity, the patient should be individualized and choice of treatment should be based on the specific findings in each case. When an embolus involves the aorta or iliac or femoral arteries, it should be treated as a surgical emergency, provided the patient's condition will permit.

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VITALLIUM TUBE METHOD FOR REPAIR OF STRICTURES OF THE BILE DUCTS

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SEVENTEEN YEARS AGO the suggestion was made that benign strictures of the bile ducts might be better repaired with the aid of a vitallium tube prosthesis. Pearse (7), in making this suggestion, wisely cautioned against overenthusiasm in the use of the method until further experience and results could be had. Most authorities on the surgery of the biliary tract, including Cole and his co-workers, Lahey (4), and Walters, have apparently abandoned use of the vitallium tube, but despite this, Pearse in 1955 (8) was able to report a favorable 15 year follow-up on the first patient in whom such a tube had been inserted, as well as 4 other favorable long term results. A rather extensive experience with use of the vitallium tube method of repair of the bile ducts has been acquired at the Mayo Clinic since its first application in 1944, and a study of the results of this experience should be helpful in determining the value of the method.

OPERATIVE SERIES

All patients who have had a vitallium tube inserted into the biliary ducts during the repair of strictures of those ducts and re-establishment of end-to-end continuity are included in this study. There are 52 such patients. Adequate follow-up information to October 1956 is available on all but 4 patients. The remaining 48 patients form the basis of this report.

The range in age of the patients in this series is typical of the range for those having disease of the biliary tract, and is from 16 to 70 years, the largest group being in the fifth decade of life. Only 9 patients are males.

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Previous operations on the biliary tract appeared to mark the onset of the stenosis in every instance except 1, and the assumption must therefore be made that injury to the ducts at operation or as a result of the operation caused the stenosis. The 1 exception was the youngest patient in the group, a 16 year old boy who sustained injury to the bile ducts from a bullet that penetrated this region.

The definitive operation in which the vitallium tube was inserted occurred from 2 months to 13 years after the surgical procedure that appeared to cause the stricture, but most commonly 6 to 18 months had elapsed. One patient had had 4 previous surgical procedures at which relief of the stricture or drainage of the biliary tree was attempted, 3 had had 2 previous attempts and 26 had had 1 previous attempt. In the remaining 22 patients, the vitallium tube was inserted at the first operation following development of the stricture.

OPERATIVE SCHEME

Before the results of this operative series can logically be given, a description of the operative plan and the results anticipated therefrom is necessary. Originally, it was hoped that the vitallium tube, situated within the bile ducts at the site of the stricture, would remain in place and continue to function more or less indefinitely. With the passage of time and the reappearance of several of these patients with recurrent biliary obstruction, and subsequent removal of their heavily encrusted and occluded vitallium tubes, there was legitimate reason to be discouraged as to the value of the technique. This, however, provided

opportunity for several interesting observations. At the time of removal of the vitallium tube a period of years after its insertion, it was noted that inflammatory reaction about the site of the stricture had subsided, scarring and induration in the wall of the duct had abated, and the mucosa had regenerated and had formed a normal-appearing unbroken ductal lining. Thus, a highly desirable end result had been achieved, although an additional operative procedure for removal of the vitallium tube had been required.

The concept naturally evolved, therefore, that were the vitallium tube method of repair of biliary strictures to have any merit, it should be planned as a two stage procedure, the first stage for insertion of the vitallium tube, and the second, at a date determined by the occurrence of occlusion of the tube, for its removal. As in our cases, a certain percentage of patients will be spared the necessity of removal of the tube for many years, and indeed may never require it.

RESULTS

In the entire 52 patients in whom a vitallium tube was inserted, there was only 1 death related to the operation, and this was in a very ill woman who had had 4 previous attempts at surgical correction of her stricture during the preceding 6 years. She died 10 days postoperatively of hepatic coma. The operative mortality rate is thus 1.9 per cent. One other patient died of "nephritis and uremia" 9 days after removal of the vitallium tube elsewhere. No other deaths were associated with surgical procedures, and no significant or unusual operative morbidity was encountered.

It has already been mentioned that 4 of the patients have been lost to complete follow-up. Of the remaining 48 patients, the final result in 7 (15 per cent) must be classified as indeterminate. In 2 of these, removal of the vitallium tube occurred less than 1 year ago, and although these patients are doing well thus far, the final result cannot yet be safely estimated. The surgical treatment of the other 5 patients deviated from the scheme outlined in that additional and probably unnecessary procedures were performed at the time of removal of the vitallium tubes, thus obscuring the final result of the operation as it is now conceived. In 4 of these 5, plastic tubes were left in the duct through the anastomosis at the time the vitallium tube was removed, and in the fifth, the operation being done elsewhere, choledochojejunostomy was performed.

The vitallium tube has never been removed from 15 patients (31 per cent). Two of these patients have died of causes unrelated to their hepatic and biliary systems. The shortest interval since insertion of these tubes is 14 months. Of extreme interest is the fact that 7 patients still have their vitallium tube in place and functioning satisfactorily 11 or more years following its insertion.

Twelve patients (25 per cent) have remained well following removal of the vitallium tube. The interval between insertion and removal of the tube ranges from 13 months to 8 years, the average interval being 5 years and 3 months. From 15 months to 10 years have elapsed since removal of the tube in these patients, with an average of 4 years and 10 months. All have had no further jaundice and no further operations, and all have been quite free of symptoms, except 1 patient who has an occasional febrile episode possibly caused by transient cholangitis.

The remaining 14 patients (29 per cent) must be regarded as representing failures of the method if critically studied, although 3 of these patients have had a satisfactory result following a second trial of the vitallium tube method of repair. The 2 deaths associated with operation have already been mentioned. Another 2 patients could possibly have been eliminated from this study, for they were operated upon early in the series, and it was then deemed impossible in them to gain sufficient length of distal duct to anastomose with the upper remnant, so

that the vitallium tube was used to "bridge the gap." This is now known to be an inadequate procedure almost always doomed to failure. The ends of the duct retract from the tube and further stenosis occurs. Adequate dissection and mobilization of duodenum and ducts should permit end-to-end anastomosis in each instance.

In 6 patients, the failure can be considered the fault of the vitallium tube which improperly performed its function. In 2, the tube had slipped down in the common duct permitting restricture above. In another 2, a fistula had developed between duodenum and bile duct, probably because of erosion of the vitallium tube. The tube in 1 patient became plugged within 3 months after insertion, thus forcing its premature removal. In the final patient of this group, the tube was spontaneously passed through the intestinal tract within a few months after insertion, with recurrence of the stricture.

In only 1 patient has further stricture developed following removal of a properly functioning vitallium tube, and the evidence for restenosis in this patient is highly questionable. She was operated upon elsewhere for symptoms of biliary obstruction, 6 years following removal of the vitallium tube, but no ductal stenosis was reported in the operative note, and the patient died 4 days later of "myocardial insufficiency."

In 2 patients, residual stricture of the duct was believed to be present at the time of removal of the vitallium tube, although the tube had been functioning properly. One of these was later treated by the Longmire operation, and the other continues to be well 8 years after insertion of another vitallium tube.

In the final patient who is considered as representing a failure by this method definite restricture of the duct did not develop, but additional stones and débris formed in the dilated biliary tree and a further operation for removal of this material was required.

Perhaps a slightly different approach to the results recorded would be of interest. In the 48 patients in whom a vitallium tube was inserted, only 6 (13 per cent) of the tubes have failed to function in the desired manner, though ultimately many have become occluded. Likewise, of the 16 patients who have had removal of the vitallium tube because of plugging, 12 (75 per cent) have had no further significant biliary or hepatic difficulty.

COMMENT

One further feature of the operative plan utilized in this series should be stressed. Only after exploration of the region of the biliary ducts is a decision for or against employment of the vitallium tube method made, for only if the end of the duct above the stricture is nonexistent or inadequate for an anastomosis with the lower end of the duct, duodenum, or jejunum is the vitallium tube used. In such instances only a small orifice in the undersurface of the liver, surrounded by scar tissue and draining bile, can be found as the remnant of the upper part of the duct. There is little hope that an anastomosis with this scar could remain patent. It is in these patients that the vitallium tube technique is indicated. The tube is introduced into the small scarred orifice above, and the lower end of the duct is drawn over the tube and sutured to the surrounding scar. The flange of the tube protrudes through the suture line to anchor it in place. The distal part of the duct may nearly always be found, though tedious search may be required. Thus this operation has been principally applied only to the cases presenting the most difficult challenge, the very group in which the incidence of failure by any method of repair is highest.

The results in this series of patients having strictures of the bile ducts compare favorably with those in other, similar series. The operative mortality rate is particularly low. Considering the fact that the cases herein reported consist largely of a selected group presenting the most difficult problems, as already described, the number of patients having a good result (56 per cent) likewise compares favorably with the number in

other series including those of Cole and coworkers, Walters, Cattell, Boren and Walters, and Lahey and Pyrtek.

The results of this study indicate that the vitallium tube method of repair of strictures of the bile ducts still deserves a prominent position in the surgical treatment of this condition. Contrary to the supposition that it is an outmoded method, it would appear to us to be the technique of choice in those most difficult cases in which no superior segment of duct can be dissected from the scarred hilar surface of the liver. It is wise, however, for surgeon and patient to regard the insertion of a vitallium tube as the first of a two stage operation, though in a few instances the second stage may never be required.

SUMMARY

Vitallium tubes have been utilized in the repair of strictures of the bile ducts in 52 patients at the Mayo Clinic, the large majority of these strictures being located high within the hilus of the liver. This operative procedure is regarded as a two stage operation, the second stage consisting of removal of the vitallium tube when and if it ceases to function. The operative mortality rate and the long term results are considered to be satisfactory. It would appear that this is a highly effective method of treating patients with biliary strictures in whom there is no upper remnant of duct extending beyond the scarred undersurface of the liver.

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THE ENDOMETRIA OF NORMAL POSTMENOPAUSAL WOMEN

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MOST OF THE STUDIES of the endometria of postmenopausal women have been based on material that could be expected to show a high incidence of abnormalities: namely, many of the specimens were obtained from patients having postmenopausal bleeding. Other studies were based on routine curettage of presumably normal postmenopausal patients but those, and frequently the majority, in which no endometrium was obtained were excluded from the subsequent data. These latter, of course, included the patients with marked atrophy of the endometrium. With the exception of one study by Speert which was based on hysterectomy specimens only, the data were obviously skewed or biased by the findings in series done in patients with postmenopausal bleeding or in those in which the "no endometrium" groups were excluded.

The present study is biased in the opposite direction since it includes only the endometria of postmenopausal women who have not been bleeding, who have not by their history received estrogens, and it includes only hysterectomy specimens. We do not know, of course, what percentage of postmenopausal women are included in this group, but we suspect that our findings are representative for the great majority of normal postmenopausal females.

REVIEW OF LITERATURE

In 1941, Novak and Richardson (9) reported that the traditional concept of the senile endometrium as extremely atrophic was borne out in only 62 of 137 cases. They subdivided their cases into four groups according to the number of years elapsed since the menopause had occurred, i.e., 2 to 5 years, 6 to 10 years, 11 to 15 years, and greater than 15 years. No correlation of appearance was found among the various postmenopausal 5 year groups. In fact, according to their data, the highest percentage of actively stimulated endometrium was in the over 15 year group. They noted that hyperplasia is often patchy in distribution. They presented the theory that the retrogressive hyperplasia pattern (those with cystically dilated glands) indicates that the last menstrual mechanisms were anovulatory and that the atrophic pattern indicates that menstruation and ovulation stopped simultaneously. However, only curettage specimens were used; those in which no endometrium was found were discarded, thus no doubt decreasing the incidence of atrophic endometria, and only 78 of 137 patients had not bled postmenopausally.

In 1944 Novak (7) repeated his theory of terminal ovulatory and anovulatory menstrual cycles and stated that the variations in postmenopausal endometrial patterns could be due to (a) types of premenopausal cycles, (b) the presence or absence of postmenopausal estrogenic stimulation, or (c) sensitivity or refractoriness of endometrial areas to the estrogenic stimulation.

Fahlund and Broders in 1946 studied the endometria of 150 normal postmenopausal uteri as a control in their study of postmenopausal patients with carcinoma of the corpus. They found 16 per cent to be atrophic, 56.7 per cent "early proliferative," and 39.3 per cent "late proliferative." These percentages are difficult to evaluate because

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of the differences in criteria used for classification. The average thickness of the endometrium in their cases was 0.3 to 0.4 of a low power field which is approximately 0.7 to 1.0 millimeter. The description of glands and stroma and the photomicrographs in their communications leave some doubt as to the criteria they used for proliferative activity.

In 1947 Gianaroli reported on 50 specimens from nonbleeding women which he divided into simple and cystic atrophy and found 15 per cent to have a cystic pattern. In 26 per cent he found telangiectasis. He stated that "cysts, simple polyps and telangiectasis are the consequence of temporary irregular reactivation of ovarian functions" and "the appearances in the endometria and ovaries examined suggest to the author that functional activity of the ovary may still be present in old age."

In 1949 Speert reported on 60 normal uteri with descensus, pointing out that (1) previous articles had included symptomatic patients and (2) tissue from curettage was used except in the Fahlund and Broders series. He used only hysterectomy specimens with microscopic sections of the entire uterine wall and from patients 2 to 35 years postmenopausal. He found cystic glands in 72 per cent of 43 patients and advanced his "retention" theory as to the causation in the following steps: (a) atrophy of lining of glands, (b) occlusion of duct, (c) casting off of cells, (d) autolysis and liquefaction, and (e) progressive enlargement or dilatation. He found only 1 case of possibly spontaneous endometrial hyperplasia. This patient had an adnexal mass that may or may not have been a hormone producing tumor. He did find occasional mitoses in glandular epithelium and questioned the necessity of estrogenic stimulation for mitoses to occur. Endometrial polyps were found in 17 per cent (10 cases), adenomyosis in 21 per cent (13 cases), and notation was made of the common occurrence of superficial veins in the endometrium.

Foix in 1952 reported on 100 curettage specimens from nonbleeding patients. He found atrophy in 86, 80 of which were cystic. He found a proliferative appearance in 10 and secretory pattern in 3. It must be pointed out, however, that this study includes patients with only 6 months of amenorrhea.

In 1953 Davies and Williams reported on 40 cases of vaginal hysterectomy for procidentia with no genital bleeding in patients 6 to 26 years postmenopausal. None had received estrogen therapy. They used Novak's classification and obtained fairly similar results. They found 40 per cent to be atrophic, 5 per cent proliferative, 25 per cent hyperplastic, and 30 per cent with "retrogressive hyperplasia."

In 1954 McBride (5) reported on 1,521 patients, none of whom had functional disorders and all had had at least 1 year of amenorrhea. Curettage produced only mucus in 1,315 and tissue in 206. In 5 year postmenopausal age groups, he found an increase in the inactive cystic gland pattern from 23.1 per cent in the 2 to 5 year group to 61.9 per cent in the over 20 year group. He also found a hyperplastic pattern in 27.5 per cent of the 2 to 5 year group and 3.5 per cent of the 16 to 20 year group. He states that there was no relationship between appearance of the endometrium in either age at menopause, type of menopause, parity, or marital status; however, the length of time after the menopause was significant. In considering his values, one must remember that the 1,315 cases in which no endometrium was obtained were not included in the statistics.

In another paper in 1955, McBride (6) summarized the previous findings and stated that 60 per cent were atrophic, 20 per cent had a diffuse inactive cystic pattern, 15 per cent had a localized cystic pattern, and that 5 per cent had a hyperplasia or proliferative pattern.

MATERIAL AND METHODS

The material for this study consisted ultimately of 335 hysterectomy specimens

from patients operated upon at the Chicago Wesley Memorial Hospital and at Passavant Memorial Hospital during the period of 1938 to 1956. The records of the laboratory of the Department of Obstetrics and Gynecology of Northwestern University Medical School and the hospital clinical and pathology records were reviewed. In all cases showing stimulated endometrium, letters were sent to the private physicians requesting information from prehospitalization records as to estrogen administration. Such were also excluded. The uteri were removed for various reasons (see Table I), usually relaxations. The microscopic sections in each case were reviewed and classified. The criteria for inclusion in the study were as follows: (1) at least 2 years postmenopausal, (2) no postmenopausal bleeding, (3) no curettage specimens, (4) no curettage prior to hysterectomy, (5) no hormone therapy within 2 years of surgery, (6) no carcinoma of cervix or endometrium, (7) no previous pelvic radium or x-ray therapy, (8) no pelvic tuberculosis, (9) no hormone-secreting tumors of the ovary except 1 thecoma with atrophic endometrium, (10) not diabetic, and (11) not severely hypertensive. All microscopic sections used included the entire uterine wall. Several cases were discarded because of slight spotting which in all probability came from trophic ulcers of the cervix.

In order to study further the possible mechanism of cyst formation, serial sections were made from 2 specimens with typical cystic glands. Fifty-six sections at 20 micron intervals, each 10 microns thick, were made in 1 case and 10 sections at intervals of 100 microns in the other.

The following data were tabulated for each specimen: (1) thickness of endometrium,[1] (2) diameter of glands[1], (3) number of glands per low power field, (4) description of stroma regarding cells, fibers, mitoses, and staining reaction, (5) description of glandular epithelium, (6) description of lining epithelium, and (7) search for spiral arteries and endometrial veins.

In an attempt to correlate histologic appearance with the number of years postmenopausal, the cases were placed into 5 year groups. The number of cases in each group is shown in Table II.

The endometria were classified as: (1) atrophic, (2) inactive cystic gland pattern, (3) hyperplastic, (4) proliferative, and (5) inactive cystic gland pattern with occasional mitoses. Our criteria of classification were modified from McBride's and were as follows:

1. Atrophic
   - Thin mucosa, up to 0.5 mm.
   - Gland diameter up to 0.15 mm.
   - Few glands
   - Fibrous stroma
   - Gland epithelium cuboidal to columnar
   - No spiral arteries
   - Thin-walled veins
2. Inactive cystic gland pattern
   - Endometrium up to 3.0 mm.
   - Average gland diameter approximately 1.5 mm.
   - 4 to 6 glands per low power field
   - Gland epithelium flattened
   - Amorphous material in glands
   - Stroma loose and myxomatous with small spindle cells
   - No spiral arteries
   - Thin-walled veins and dilated capillaries present
3. Hyperplastic
   - Thick endometrium, up to 6.0 mm.
   - Numerous glands, up to 20 per low power field
   - Gland diameter 0.13 to 0.6 mm.
   - Columnar epithelium with basophilic cytoplasm
   - Variation in size of glands
   - Cellular stroma
   - Mitoses present
4. Proliferative
   - Endometrium averaging 1.0 mm.
   - Gland diameter approximately 0.2 mm.
   - Regularity in size of glands
   - Mitotic figures present
5. Cystic gland pattern with mitoses
   - Same as No. 2 except with occasional mitoses

RESULTS

Table I indicates the reasons for surgery subdivided into the 5 year groups. If postoperative diagnoses had been used, the number of fibroids in the 2 to 5 and 6 to 10 year groups would have been increased be-

[1]The width of various power microscopic fields was calibrated and used as the frame of reference for these estimations.

TABLE I.—REASONS FOR SURGERY

Age group, yrs.	*No. of specimens*	*Prolapse or cystourethrocele, per cent*	*Ovarian tumor, per cent*	*Myoma, per cent*	*Miscellaneous,* per cent*
2–5	79	66.7	16.5	2.5	15.2
6–10	91	80.2	14.3	0.0	5.5
11–15	69	88.4	8.7	0.0	3.0
16–20	54	74.1	11.1	0.0	7.5
21–25	26	86.2	15.4	0.0	0.0
26–30	13	92.3	7.7	0.0	0.0
Over 30	3	33.3	66.7	0.0	0.0

*Includes "abdominal mass" (9), pain (7), repeatedly positive Papanicolaou smear (2), stenosis of cervix (1), dyspareunia (1), carcinoma of vagina (1), adenomyosis (1), and recurrent cervical polyps (1).

cause the majority of those listed under "abdominal mass" and "pain" turned out to be fibroids with degeneration. The majority of indications consisted of prolapse of the uterus or cystourethrocele. Ovarian tumors constituted a significant proportion of indications in all age groups. The preoperative diagnosis of myoma was rarely made, but "abdominal mass" and "pain" were frequent indications in the patients less than 20 years postmenopausal.

Table II shows the endometrial findings in each 5 year group as classified by the criteria mentioned previously. The percentage of patients with simple atrophic endometrium decreased as the number of years postmenopausal increased. A parallel increase in the percentage of patients with an inactive cystic pattern was found. The simple atrophic and inactive cystic patterns were the only types of endometrium which showed any correlation with age. The inverse relationship between these two patterns indicates that as the number of years after the menopause increases, the number of atrophic patterns which become cystic increases, probably because of blocking of the ducts of the glands with inspissated secretion and sloughed cells and subsequent slow cystic dilatation.

The percentage of endometrial polyps in the cystic and atrophic patterns did not change and showed no correlation with postmenopausal age.

Only 3 examples of hyperplasia were found. Two of these were in the 2 to 5 year group. The past history and preoperative records of these patients were carefully examined and none of these women had received hormones. The prehospitalization record in the 1 case in the 11 to 15 year group was not available; the possibility that she had received hormones cannot be completely ruled out.

Only 1 patient with endometrial proliferation was found and she had not been given hormones.

Two patients satisfied the criteria of cystic pattern but occasional mitoses were present in the glands. One of these was in the 6 to 10 year group and the other in the 11 to 15 year group. These patients had not received hormone therapy and the stimulus for the occasional mitoses is unknown. No mitoses were found in any instance of the simple atrophic pattern.

Table III shows the incidence of associated disease subdivided into the 5 year groups. In many cases these were asymptomatic conditions which were not the reason for surgery. No change was noted in the incidence of polyps with postmenopausal age. The number of ovarian tumors was fairly constant and showed no correlation

TABLE II.—DISTRIBUTION

Age group, yrs.	*No. of specimens*	*Simple atrophic, per cent*	*Cystic atrophic, per cent*	*Hyperplastic per cent*	*Proliferative, per cent*	*Cystic with mitoses, per cent*
2–5	79	69.6	26.6	2.5	1.3	0.0
6–10	91	56.1	42.9	0.0	0.0	1.1
11–15	69	37.6	59.4	1.5*	0.0	1.5
16–20	54	38.9	61.1	0.0	0.0	0.0
21–25	26	34.6	64.3	0.0	0.0	0.0
26–30	13	30.8	69.2	0.0	0.0	0.0
Over 30	3	0.0	100.0	0.0	0.0	0.0
Total	335	49.6	48.9	0.9	0.3	0.6

*Complete preoperative records not available on this 1 patient.

TABLE III.—ASSOCIATED DISEASE

Age group, yrs.	*No. of specimens*	*Endometrial polyps, per cent*	*Fibroids, per cent*	*Ovarian tumors, per cent*	*Adenomyosis, per cent*	*Endometriosis, per cent*
2–5	79	19.0	43.0	19.0	11.4	1.3
6–10	91	14.3	37.4	17.6	7.7	1.1
11–15	69	17.4	26.1	8.7	5.8	2.9
16–20	54	18.5	16.7	11.1	9.3	1.8
21–25	26	15.4	11.5	19.2	7.7	3.8
26–30	13	15.4	7.7	7.7	0.0	0.0
31–35	2	0.0	0.0	50.0	0.0	0.0
Over 35	1	100.0	100.0	100.0	0.0	0.0
Total	335	17.0	29.9	15.2	8.0	1.8

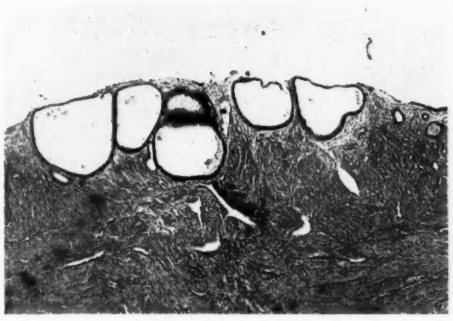

FIG. 1. Cystic atrophic pattern. × 44.

FIG. 2. Simple atrophic pattern. × 45.

with postmenopausal age. The incidence of adenomyosis and endometriosis was low and showed no consistent change. The percentage of fibroids, however, correlated well with postmenopausal age and revealed a progressive decrease as the number of years postmenopausal increased.

The distribution and types of ovarian tumors are shown in Table IV. There was no correlation of type of tumor with postmenopausal age. The cystoma-cystadenoma group was the most frequent tumor found.

The serial sections mentioned previously were studied carefully in a search for cysts that were completely within our sections. Several isolated cysts were followed completely and in no instance was it possible to find any suggestion of a duct or any connection with other glandular structures. Furthermore, occluded ducts were not found.

DISCUSSION

As previously noted, the cystic gland pattern (Fig. 1) increased significantly with age (Table II) from 26.6 per cent in the 2 to 5 year group to 61.5 per cent in the over 20 year groups. This observation agrees with the findings of Speert and of McBride, both of whom found a high percentage of cystic gland pattern. Simple atrophic pattern (Fig. 2) correspondingly decreased with age from 69.6 per cent in the 2 to 5 year group to 30.48 per cent in the over 20 year groups. This fact seems to indicate that more simple atrophic endometria become cystic as the number of years postmenopausal increase. In our opinion, the indication is that the pathogenesis of the cystic gland pattern is simple obstruction of the ducts of glands with progressive dilatation of the glands rather than that it is initiated by anovulatory climacteric menstrual cycles as suggested by Emil Novak. If the latter mechanism were the cause, the cystic gland pattern would not show an increase with age and the simple atrophic pattern should not decrease. Obviously, we believe that Speert's explanation is correct.

TABLE IV.—DISTRIBUTION OF OVARIAN TUMORS

Type	*Postmenopausal years*							
	2–5	*6–10*	*11–15*	*16–20*	*21–25*	*26–30*	*31–35*	*Over 35*
Serous cystoma and cystadenoma	6	1	1	4	2		1	1
Papillary serous cystadenocarcinoma	1	1						
Pseudomucinous cystadenoma	5	3			1			
Teratoid—cystic, benign	5				1			
Teratoid—malignant					1			
Fibroadenoma	1		1			1		
Fibroma		1	1	1				
Thecoma				1				
Hemangioma	1							
Brenner tumor	1							

FIG. 3.

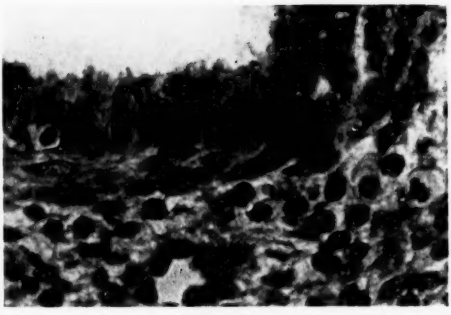

FIG. 4.

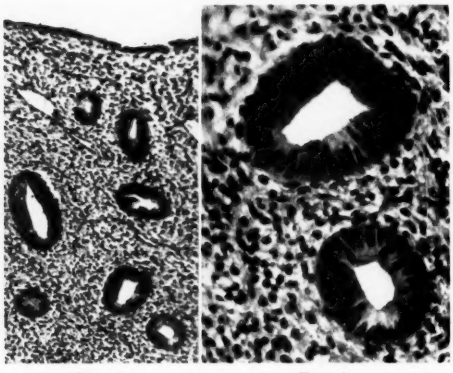

FIG. 5.

FIG. 6.

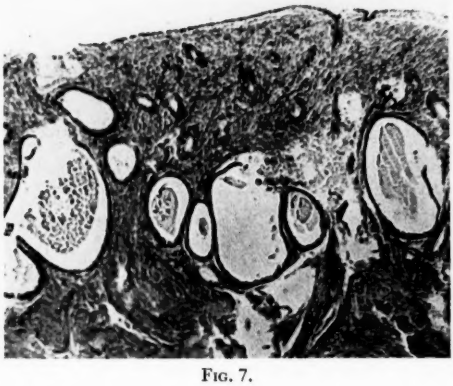

FIG. 7.

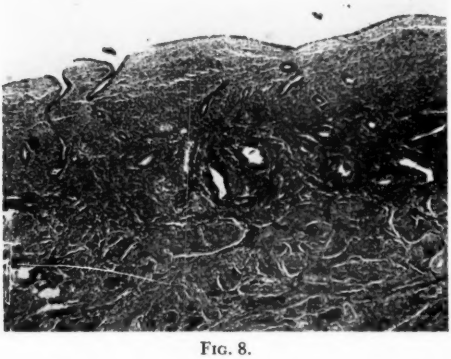

FIG. 8.

FIG. 3. Photomicrograph showing hyperplasia pattern. × 50.

FIG. 4. Photomicrograph showing hyperplasia pattern. × 618.

FIG. 5. Photomicrograph showing proliferative pattern. × 80.

FIG 6. Photomicrograph showing proliferative pattern. × 465.

FIG. 7. Surgical castration 40 years prior to hysterectomy (at age 20). × 50.

FIG. 8. Specimen from patient who received hormones during climacteric. × 40.

Only 3 of 335 cases were found to be hyperplastic (Figs. 3 and 4). This observation is in sharp contrast to the findings of previous workers except for Speert who found no cases of hyperplasia which could not be explained on the basis of either exogenous hormone or a hormone-secreting tumor.

We are also in agreement with Speert's finding in our own 2 cases of cystic gland pattern with occasional mitoses. Except for the mitoses, which were in both the gland epithelium and the stroma, the cases satis-

fied all of the criteria for the atrophic cystic gland pattern. We seriously doubt that estrogens are a *sine qua non* for any and all mitoses in the endometrium. After all, cells in the atrophic endometrium do not live indefinitely and a few must be slowly replaced. How else but by mitotic division of more healthy or less debilitated cells?

The number of cases of proliferative endometrium (Figs. 5 and 6) was also low; in fact, there was only 1. In all of the other cases found in our original material (41) some hormone had previously been received exogenously. Blood and urine hormone levels were not determined in either the 3 hyperplastic or the 1 proliferative case, and although the ovaries were atrophic and showed no evidence of activity, obviously there must have been either postmenopausal estrogen secretion by the ovaries or by the adrenals to stimulate the endometrium. Our data, however, certainly do not support any of the various claims, or inferences, that there is an appreciable amount of estrogens produced in the normal postmenopausal female.

One interesting case of a 66 year old patient who had a hysterectomy for prolapse was not included in our data since she had received stilbestrol for 2 days prior to surgery. In 1906 at the age of 20, 40 years prior to hysterectomy, she was subjected to a bilateral oophorectomy, supposedly for amenorrhea. There is no doubt that both ovulation and ovarian estrogen secretion ended simultaneously at that time, yet the endometrium showed a marked cystic gland pattern. The endometrium was 0.5 to 0.6 millimeter thick and contained glands approximately 0.2 to 0.3 millimeter in diameter with an occasional gland as large as 0.4 millimeter. The stroma was markedly fibrotic and no mitoses were present (Fig. 7). The preoperative hormone therapy was not given long enough to result in this pattern. Another patient who had estrogen therapy during the climacteric exhibited a very atrophic endometrium (Fig. 8). It seems logical to assume that such therapy would have the same effect as a terminal anovulatory cycle; hence it would be expected that the endometrium would be cystic. We believe that this observation constitutes additional evidence against an anovulatory menopause as the mechanism for cystic gland formation.

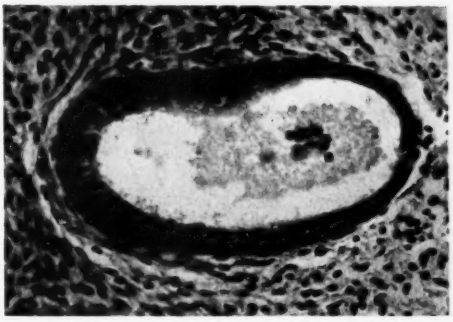

FIG. 9. Nucleated cells in cystic gland from case of cystic atrophic pattern. × 443.

Two interesting findings in the associated pathologic conditions are worth mentioning (Table III). The percentage with fibroids decreased significantly with age, i.e., from 43 per cent in the 2 to 5 year group to 7.7 per cent in the 26 to 30 year group. An explanation for this is not apparent to us although the difference in frequency of fibroids, in part, may be related to the indications for operating as some patients in the earlier age groups were operated upon for degenerating fibroids. The second finding worthy of comment is the low percentage of adenomyosis (Table III). It is much lower than that reported by previous workers, possibly because of different criteria for the diagnosis of adenomyosis uteri; with us the ectopic endometrium must extend at least 1 low power field below the endometrial-myometrial junction.

SUMMARY AND CONCLUSIONS

1. The endometria of hysterectomy specimens from 335 women who were 2 to 35 years postmenopausal were examined. None of these patients had been bleeding and none had received estrogens.

2. In only 4 instances was it believed that the endometrium showed evidence of stimulation. Three of these were hyperplastic and 1 was in the proliferative phase.

3. The remaining endometria showed either a simple atrophy or inactive endometrium with cystic glands. With an advancing number of years since the last menstruation, the cystic pattern became progressively more common.

4. Areas from 2 specimens were serially sectioned. Isolated cystic glands were found to have no communication with a duct or with any other gland structure.

5. The progressive increase in the incidence of the cystic pattern with advancing years after the menopause and the failure to demonstrate communication with a duct strongly suggest that these cystic changes are merely a slowly progressive distention phenomenon and are not an aftermath of "Swiss cheese" hyperplasia during the climacteric.

6. Associated disease was also studied and tabulated. The incidence of myomas decreased with postmenopausal advancing years. That of endometrial polyps did not change nor did that of adenomyosis, endometriosis, or ovarian tumors.

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THROMBO-ENDARTERECTOMY OF THE CAROTID BIFURCATION AND THE INTERNAL CAROTID ARTERY

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REPORTS IN THE LITERATURE indicate the commonness of internal carotid artery occlusion in patients suffering from a stroke syndrome. Since 1950, we have encountered 125 such cases proved by angiography (5, 10). Approximately 60 carotid arteries were exposed and the pathologic lesions identified. In complete occlusions, in all but 3 patients the distal portion of the artery remained occluded after removal of even a recent thrombus. In most cases, the artery was firmly obstructed with an organized thrombus. A section from the artery was usually taken and a cervical sympathectomy then was done in conjunction with the arterectomy. Results have not clearly indicated substantial benefits from this management. It has appeared that the surgical treatment for occlusive disease of the carotid artery must be undertaken earlier, before total obstruction occurs. Attention is, therefore, directed first to the diagnosis of partial atheromatous occlusions, then to an effective surgical method of treatment.

DIAGNOSIS

The diagnosis of partial atheromatous occlusion is by adequate and accurate angiography of the carotid bifurcation in the neck. In patients who may have repeated attacks of weakness or sensory abnormalities in one-half of the body, associated in some instances with lasting weakness or sensory abnormality with or without an attack of unconsciousness, angiography is indicated. By angiography, it is often possible to establish reliably the occurrence of atheromatous degeneration of the internal carotid artery, which can then be correlated with the clinical evidence of a reduction in blood flow, manifested by neurologic symptoms and findings. Usually, the major stenotic lesion is at the beginning of the internal carotid artery near the bifurcation. These atheromatous changes may be segmental and diffuse. There are a number of segmental lesions, so that excision of such a lesion may be of value. In angiography, care must be taken to avoid interpreting an artefact as an occlusion, or stenosis.

A second method of investigation is by carotid artery compression. In patients who have a partial occlusion of the carotid bulb and internal carotid artery, compression of the opposite carotid bulb may result in syncope associated with weakness and convulsive movements on the side opposite the compression. Syncope due to a carotid sinus syndrome, or an insufficiency in the basilar artery distribution, also has to be remembered. Use of adequate doses of atropine helps rule out a sensitive carotid sinus.

When the presence of a cerebrovascular insufficiency due to a partial carotid occlusion, with evidence of impending or already existent cerebrovascular failure (i.e., hemiplegia), has been demonstrated by both angiographic studies and compression tests, surgical treatment should be considered.

SURGICAL TREATMENT

Surgical experience with endarterectomy for segmental arteriosclerosis of the lower limbs and the large abdominal and pelvic arteries has increased during the past few years. Among others, Cannon and Barker, Luke, and Wylie and Gardner discuss its use in the management of segmental obliterative diseases of the lower limbs. Crawford

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Aided by the Kresge Foundation.

TABLE I.—SUMMARY OF EXPERIENCE WITH ENDARTERECTOMY

Case No.	*Name*	*Sex Age*	*Preoperative neurostatus*	*Angiogram*		*Postoperative anticoagulative therapy*	*Results*
				Preop.	*Postop.*		
1	Devers	W.M. 59	Attacks of confusion left hemiparesis	Stenosis	Patent	6 weeks	Improved (Fig. 2)
2	Clark	W.F. 57	Right hemiparesis confusion	Stenosis	Patent	2 weeks	Improved (Fig. 4)
3	Thompson	W.M. 65	Left hemiplegia	Stenosis int. carotid above bifurc.	Patent	6 weeks	Improved (Fig. 5)
4	Cable	W.M. 55	Right hemiplegia	Stenosis 1 cm. above bifurc.	Complete occlusion	4 months	No charge
5	Lawless	W.M. 53	Left hemiparesis	Stenosis just above bifurc.	Complete occlusion	4 months	Improved

and DeBakey, Laufman, Holf, Bernhard, and Trippel, and others discussed the value of bypass hemografts in such cases. Endarterectomy of the carotid bifurcation and internal carotid artery has been described by Strully, Hurwitt, and Blankenberg, Gass and Smathers, Rob and Wheeler, Cooley, Naaman, and Carton, and others.

Several surgical techniques toward evaluating a suitable method of management of the partially occluded carotid artery have been tested, both in the laboratory and in clinical trials. These have included, first, the use of arterial homologous grafts; second, the use of external carotid artery as a shunt; third, prosthesis; and fourth, thrombo-endarterectomy (intimectomy).

It has been found that the use of a graft is technically difficult because the atheromatous and narrowed arterial wall of the distal segment is usually unsatisfactory for anastomosis, and the restricted field of work immediately under the jaw, also limited by the twelfth nerve, makes adequate exposure of the internal carotid artery difficult. Use of the external carotid artery as a shunt, in addition, sacrifices this important source of collateral circulation. The use of synthetic tube graft (crimped nylon), which could be inserted into the artery through a linear incision after removing the atheromatous proliferations, has been evaluated in 20 dogs and has also been attempted in the human; results have been discouraging. In the experimental animal, eventual occlusion of the vessel by aggregates of intimal proliferation was noted. We have used endarterectomy in 5 patients; the angiogram 2 to 4 months after the surgery has revealed patency in blood flow in 3, and occlusion of the vessels in 2. In Table I, the important aspects of this limited experience are summarized.

Preoperative compression tests are used before thrombo-endarterectomy. Compression tests help evaluate the extent of the insufficiency, and demonstrate any untoward effects to be expected from the complete occlusion of the stenosed vessel during operation. In the 5 patients, we have encountered no difficulties on compression of the carotid bifurcation on the side of the stenosis, indicating that there was enough collateral circulation to help supply the distribution of the stenosed side. If compression for 10 to 12 minutes causes no increase in the signs and symptoms in such a case, then occlusion of the vessel in normal temperatures is not dangerous in management. If, on the other hand, compression tests show that there is increased weakness of the opposite half of the body from the partially occluded side, then repeated compression over a period of several days may result in an improvement in this state. If not, such a patient should be operated upon under hypothermic conditions to minimize the effects of the ischemia on the brain. The acutely paralyzed patient who shows an occluded carotid on emergency angiography should, of course, be operated upon under hypothermic conditions.

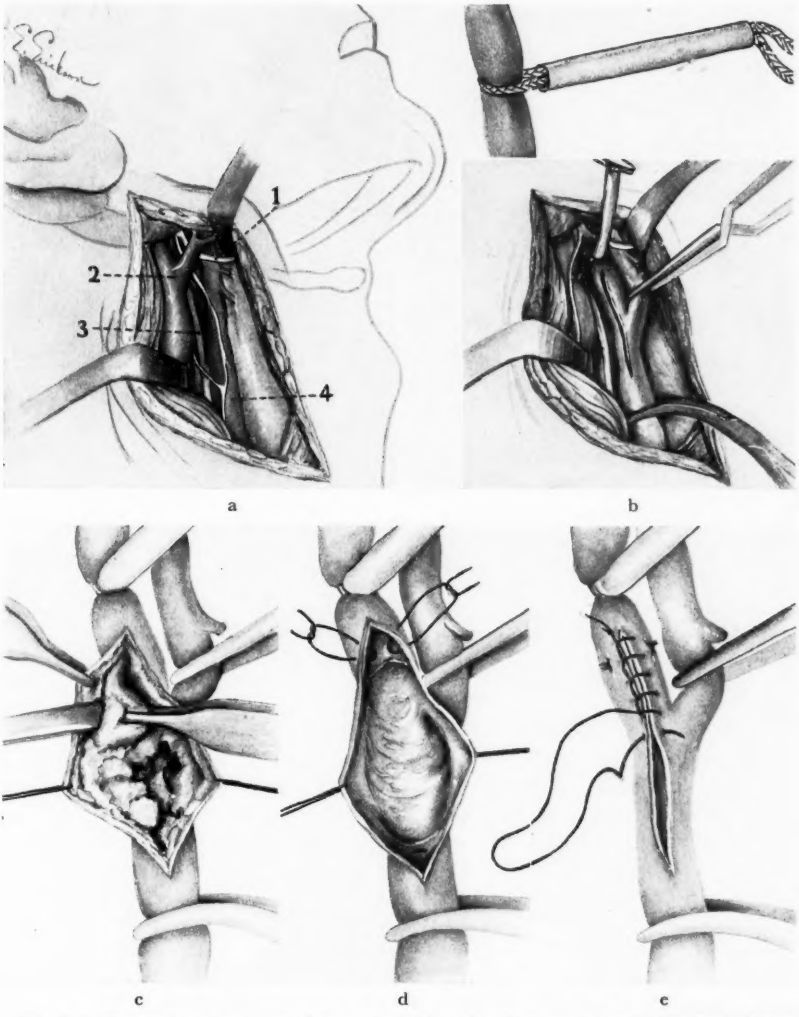
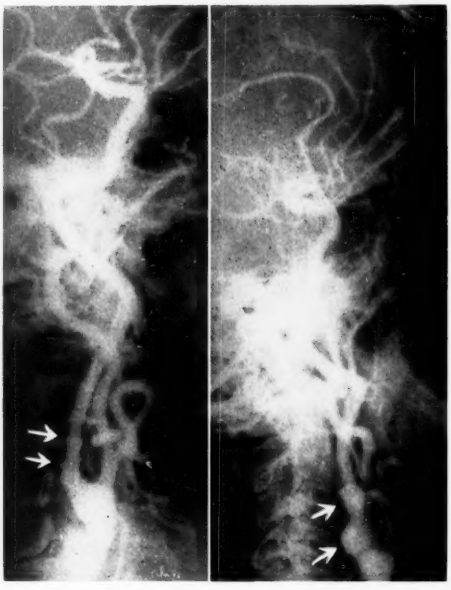


FIG. 1. a, The pertinent anatomy of the neck: *1*, Hypoglossal nerve and ansa hypoglossi. *2*, Jugular vein and deep facial tributary. *3*, Vagus nerve. *4*, Common carotid and internal and external arteries. b, Above, The method of occluding vessel with a tape passed through a tube. Below, Carotid bifurcation and internal carotid incised for endarterectomy. c, d, e, The technique for removal of the atheroma and closure. Note that the internal edge is sutured to the adventitia both above and below.

The operation may be done under intratracheal anesthesia with infiltration of the skin locally with xylocaine solution. An adequate incision is used to expose the carotid bulb and internal and external carotid arteries. To extend the exposure of the internal carotid artery as superiorly as possible, it is usually necessary to cut the deep facial vein emptying into the internal jugular. This procedure also permits the forward retraction of the twelfth cranial nerve. In some instances, it may be necessary to cut



a b

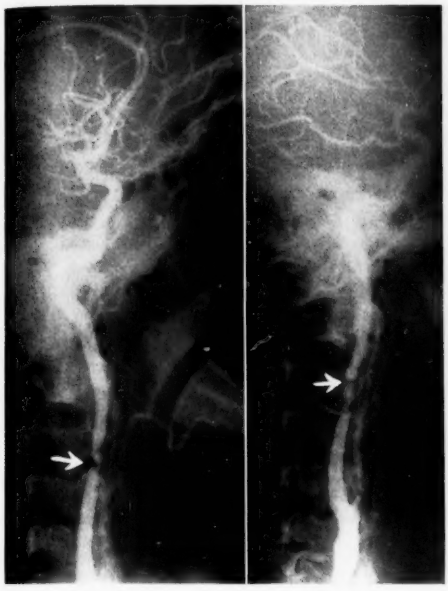
FIG. 2.

FIG. 2. a, Atheroma of internal carotid artery before excision; b, after excision. The latter was taken 3½ months after operation.

FIG. 3. Atheroma removed from patient in Figure 2.

FIG. 3.

the ansa hypoglossi. When exposing the common carotid, the bifurcation, and the internal and external carotid arteries, care is taken not to remove the adventitial lining in order to have enough of this left to support the vessel wall after the removal of the atheroma. The vagus nerve is identified and freed from the carotid. Umbilical tapes may be useful in mobilizing the common, internal, and external carotid arteries. Suitable arterial clamps are then used; we use long handled clamps bent in a way so that they lie outside the field of operation. To occlude the distal portion of the internal carotid artery, a No. 4 braided silk, or a tape, may be placed around the artery, then passed through a section of polyethylene tubing to form a loop and tightened about the vessel. This provides more room for working (Fig. 1). If a hypersensitive carotid sinus reflex is present, novocain solution may be infiltrated about the bulb before any manipulations are begun. Such a patient also should be protected with the use of 1/50 to 1/100 grain of atropine sulfate. In these cases, pumping of blood from the common carotid to the internal carotid, distal to the clamps, has not been necessary because of the restricted flow which already exists. Linear incision is then made into the artery through the area of the stenosis. Beginning on the wall of the incision, the plane of cleavage is determined with small forceps and scissors. This plane represents the lamina of the internal elastic membrane and the stenotic area may be loosened and then excised in pieces. After flushing out the area with saline and heparin solution, continuous horizontal mattress stitches of No. 4-0 waxed arterial suture are used to close the incision. Before complete closure, all air and other matter are permitted to escape



a b

FIG. 4. a, Internal carotid artery occlusion before the excision of the atheroma, and b, 2 months after excision of the atheroma.

a b

FIG. 5. a, Narrowing of internal carotid artery as it branches off the common carotid. b, Angiogram 13 weeks later showing absence of the stenosis.

out of the vessel to be closed. The clamp on the distal portion of the internal carotid artery is first removed, then that on the external carotid artery, and then that on the common. A strip of gelfoam is held over the sutured vessel; temporary pressure, for a minute or so, with a cottonoid pad results in a dry field. The atheromatous plaque may be a hill of atheroma extending into the vessel lumen, or it may be a diffuse lesion extending along the interior aspect of the vessel. As may be seen in Figure 3, the removed atheromatous plaque was almost a cast of the interior of the bifurcation; however, at the beginning of the internal carotid artery, there was a definite bulging of the atheroma into the lumen.

If this method of management does not work because of the extreme friability of the tissues, the use of a homologous graft is suggested. As may be seen in Figure 2, following the removal of the atheroma at the bifurcation, some enlargement of the bulb and the proximal portion of the internal carotid has occurred. Whether or not this may develop further to form a large aneurysm is to be seen in the future. It is believed that repeated angiograms in these patients are definitely indicated to note the patency of the vessels.

We have used anticoagulant therapy beginning several hours after the operation and continued its use for 2 to 6 weeks. Possibly this should be continued for many months or forever, as suggested by Rob and Wheeler. Future experience will help decide a rational use for such drugs.

SUMMARY

In a clinical syndrome as unpredictable as cerebrovascular failure, results of thrombo-endarterectomy are difficult to evaluate, and only after many cases observed over a period of years by many neurosurgeons can

one be fairly sure of the value and the efficacy of this procedure. The mechanical removal of occlusive masses to maintain the cerebral circulation and to delay cerebrovascular failure may be valuable until atheromatous disease of vessels can be prevented or ameliorated by other means.

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PREVENTION OF EXPERIMENTAL LUNG METASTASES WITH TRIETHYLENETHIOPHOSPHORAMIDE (ThioTEPA)

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THE OCCASIONAL APPEARANCE of disseminated metastases very shortly after cancer surgery is distressing to the surgeon. There is frequently a strong suggestion that the operation was responsible. Recently, interest has developed in the use of adjunctive chemotherapy to prevent such metastases. Cruz and McDonald have demonstrated the effectiveness of nitrogen mustard and triethylenethiophosphoramide (ThioTEPA) in preventing rat liver metastases of Walker carcinosarcoma. On the basis of this work, they began a program of nitrogen mustard therapy given in the immediate postoperative period. In addition, the Surgical Clinical Studies Panel of the Committee on Chemotherapy of the National Advisory Cancer Council initiated a statistically oriented, long-term, co-operative study of the effects of chemotherapeutic agents on the survival rates and clinical course of cancer patients undergoing surgery for potentially curable lesions.

Such treatment is based on the assumption that metastases are stimulated by surgical intervention. Neither Engel nor Moore has demonstrated an increased number of human tumor cells in the blood following surgical manipulation. Schatten and Kramer (8) have shown that surgical stress per se has no apparent effect on the number of developing metastases in experimental animals. However, others have shown that tumor massage in experimental animals results in an increase in the number of metastases. Furthermore, Schatten (7) has shown that the presence of the primary tumor exerts an inhibitory effect on the development of metastases. With excision of the primary tumor more and larger metastases occur than in animals whose primary was not removed. Thus there is experimental support for the concept that surgical removal of a malignant neoplasm is associated with an increase in the number of metastases.

ThioTEPA has been used extensively in patients with advanced cancer. Although it is a bone marrow depressant, its toxicity can be controlled by adjusting the size and spacing of doses in accordance with the results of frequent blood counts. Serious complications from its use have not been observed at this hospital. It is relatively stable, nonirritating to the tissues, and free of acute toxicity symptoms such as nausea and vomiting. Permanent cures have not been reported with its use, but there have been several reports of its effect in diminishing the size of metastatic lesions and improving the clinical course, especially in cases of breast carcinoma. It is possible, therefore, that the drug might be employed with greater hope of permanent cure if it were administered at the time of surgery against fresh implants when they are still of microscopic size.

It is the purpose of this study to evaluate the effectiveness and optimal treatment schedule of ThioTEPA in preventing artificial melanoma metastases in mice. Studies on the effectiveness of ThioTEPA against tumors in other animals are also presented. The relevance of these findings to the clinical situation is discussed.

From the Surgery Branch, National Cancer Institute, National Institutes of Health, Public Health Service, United States Department of Health, Education, and Welfare.

TABLE I.—TREATMENT OF ARTIFICIAL S-91 METASTASES WITH THIOTEPA

Exper. No.	Day of Thio-TEPA admin.	Treated: Total No. tumors	Treated: No. mice	Treated: Mean No. tumors per mouse	Controls: Total No. tumors	Controls: No. mice	Controls: Mean No. tumors per mouse	Treated takes*	Per cent effective
1	0	340	20	17 ±8.5**	2271	10	227 ±29	17/20	92.5
2	0	37	5	7.4 ± 5.7	1369	5	274 ±78	4/5	97.3
3	0	12	5	2.4 ± 0.8	795	5	169 ±31	4/5	98.5
4	0	155	24	6.5 ± 3.0	1564	16	98 ±12	22/24	95.4
5	0	14	10	1.4 ± 0.4	426	10	4.3 ± 7.8	8/10	96.7
6	0	51	10	5.1 ± 1.7	1274	6	212 ±21	9/10	97.6
7	0	32	8	4.0 ± 1.5	1366	11	124 ±16	7/8	96.8
8	0	246	8	31.0***	3955	16	247 ±46	-***	87.5
									95.4 av.
2	1	4	5	0.8 ± 0.1	1369	5	274 ±78	4/5	99.7
4	1	7	5	1.4 ± 1.2	1564	16	98 ±12	2/5	98.6
8	1	37	8	4.6***	3955	16	247 ±46	-***	98.1
									98.8 av.
2	2	0	5	0.0 ± 0.0	1369	5	274 ±78	0/5	100
4	2	0	4	0.0 ± 0.0	1564	5	98 ±12	0/4	100
7	2	29	9	3.2 ± 1.3	1366	11	124 ±16	8/9	97.4
8	2	59	7	8.4 ± 2.5	3955	16	247 ±46	7/7	98.5
									99.0 av.
2	3	7	5	1.4 ± 1.0	1369	5	274 ±78	2/5	99.5
7	3	53	9	5.9 ± 1.1	1366	11	124 ±16	9/9	95.2
8	3	52	8	6.5 ± 2.8	3955	16	247 ±46	7/8	97.4
9	3	121	8	15.0 ± 5.2	4620	8	578 ±56	8/8	97.4
									97.4 av.

Detailed sample of experimental results.
Dose—10 micrograms per gram of body weight.
* =Treated animals with some lung tumors/total number treated animals. (Control animals all had tumor.)
** =Standard error of the mean.
***=Only total number of tumors in group counted.

MATERIALS AND METHODS

Transplantable animal tumors used in this study were as follows:

Melanoma S-91, a soft, dark brown, moderately slowly growing pleomorphic melanoma. It is strain specific for DBA mice and their f_1 hybrids.

Sarcoma 37, a rapidly growing tumor which grows in both the ascites and solid forms in all mouse strains.

Walker carcinosarcoma 256, a rapidly growing tumor which grows in all strains of rats.

V2 carcinoma, a non strain-specific, rapidly growing rabbit tumor.

The animals used in this study were as follows:

CDBA female mice, 1 to 6 months of age, in experiments with S-91 melanoma.

NIH white female mice, 1 month of age, in experiments with S-37 tumor.

Fifty gram Sprague Dawley female rats in experiments with Walker carcinosarcoma 256.

One kilogram New Zealand white rabbits in experiments with V2 carcinoma.

THIOTEPA was supplied in the crystalline form. It was diluted with normal saline shortly before use to concentrations varying from 0.1 to 1.0 per cent.

The experimental system used with S-91 tumor will be discussed elsewhere in greater detail (2). Donor animals with intramuscular thigh tumors were sacrificed. An estimated 1 gram of tumor was passed through the screen of a cytosieve with 10 cubic centimeters of physiologic saline and a few heparin crystals. A suspension of separate cells and minute tumor fragments resulted. All mice were inoculated via the tail vein with 0.05 cubic centimeter of this tumor suspension. The mice were then arranged in treatment groups in such a way as to avoid systematic errors. Injections of THIOTEPA were given at planned times before or after tumor inoculation. It was administered intraperitoneally in various doses from 1 to 20 micrograms per gram of body weight. Thirty micrograms per gram constituted the maximum tolerated dose. Ten micrograms per gram were used as

the standard dose although mild weight loss was noted with its use. Animals were sacrificed at 28 days from the time of intravenous inoculation of tumor. Only the lungs contained metastases. The lungs were excised and the discrete, black, spherical tumors (Fig. 1) were counted with the aid of a binocular loupe. The potency of the inoculum varied considerably from one preparation to another so that the control number of tumors ranged from 40 to 1,100 tumors per mouse in different experiments. However, the variation within each experiment was sufficiently small so that differences of 50 per cent were detected with statistical assurance. The average number of lung tumors per treated mouse was divided by the average number per control mouse and the resulting fraction converted to per cent. This value was subtracted from 100 to obtain a "per cent effectiveness" for the particular treatment. This calculation made possible direct comparison of results in different experiments despite the differences in control levels.

In experiments with S-37 tumor, mice were inoculated intravenously with dilute, heparinized S-37 ascitic fluid, treated intraperitoneally with THIOTEPA and sacrificed for lung tumor counting at 9 days.

In Walker carcinosarcoma experiments, rats were inoculated with 0.05 cubic centimeter of cytosieved inoculum, treated with intraperitoneal THIOTEPA and sacrificed for counting at 16 to 17 days.

In V2 carcinoma experiments, rabbits were inoculated in the ear vein with cytosieved inoculum. Animals were treated intravenously with THIOTEPA and sacrificed for counting at 14 days. Because of the large number of tumors only the flat side of the large left lobe was counted.

In both the rat and rabbit, the maximum tolerated dose was 5 micrograms per gram, much lower than that found for mice.

The metastases from tumors other than S-91 were more difficult to detect and count because of their light color and tendency to conglomerate into masses of several tumors.

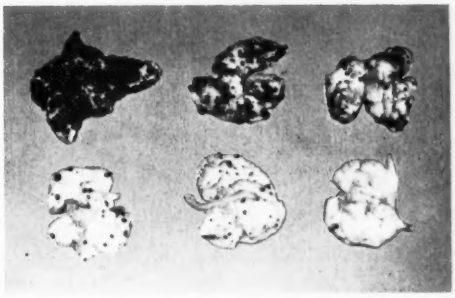

FIG. 1. Photograph demonstrating the discrete, black, countable tumors present in the lungs of animals receiving intravenous S-91 melanoma. The lung in the upper left hand corner is from an untreated animal. The other lungs are from animals who received (L. to R.) 3, 6, 9, 12, and 15 micrograms per gram of THIOTEPA on the day of inoculation.

RESULTS

The data presented here summarize the results of 49 experiments involving 3,600 animals performed over the space of 2 years. The large number of observations prevents publication in full of these data. A representative sample of such results is given in Table I. The results are quite consistent from experiment to experiment.

The results of the treatment of intravenous melanoma metastases with THIOTEPA on the day of inoculation are shown in

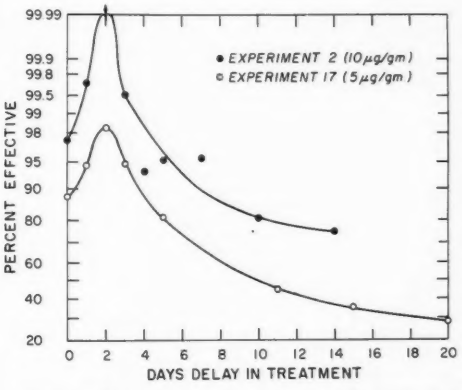

FIG. 2. Variation of effectiveness of THIOTEPA with delay in therapy. Day 0 is the day of intravenous S-91 inoculation.

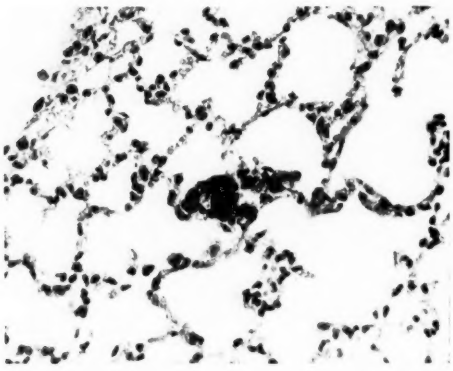

FIG. 3. Damaged S-91 tumor in alveolar septum of an animal who received heavy dosage of THIOTEPA. Coarse clumps of melanin are seen. Cellular detail is difficult to distinguish. Hematoxylin and eosin, ×265.

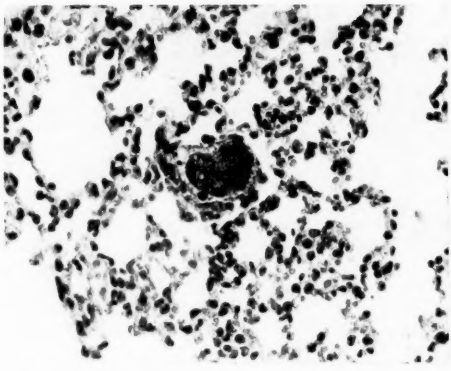

FIG. 4. Photomicrograph of a tumor giant cell occurring in the lung of an animal treated with heavy dosage of THIOTEPA after intravenous inoculation with S-91 melanoma. Hematoxylin and eosin, ×265.

Table II. Increasing doses were increasingly effective.

The effects of delaying the day of treatment are shown in Figure 2. With all doses tested, effectiveness increased to a maximum on the second day and then diminished. An effect was still detectable after a delay of 2 weeks. Thus, under optimal conditions, THIOTEPA was highly effective. Some animals which, if untreated, might have been expected to have 100 or more tumors had none (Table I).

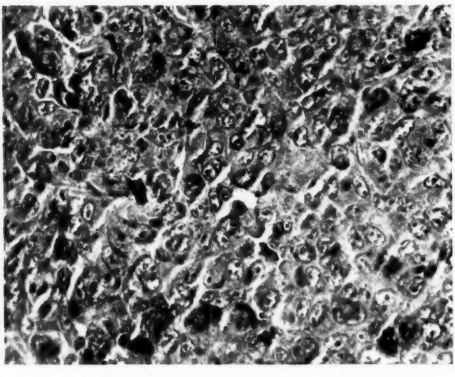

FIG. 5. Photomicrograph of a section through an untreated pulmonary metastasis of S-91 melanoma. Cells typical of a growing malignant tumor are readily distinguished in contrast to Figures 3 and 4.

Pretreatment with THIOTEPA within 30 minutes before tumor inoculation had about the same effect as treatment immediately after injection. Treatments given more than 30 minutes before tumor inoculation resulted in decreasing effectiveness, with all effectiveness gone by 2 hours with doses of 5 and 10 micrograms per gram. A dose of 15 micrograms per gram still had some residual effect at 2 hours (Table III).

A series of experiments was done to determine the effects of repeated treatments with divided doses which individually were only moderately effective. The results are presented in Table IV. These generalizations can be made:

Each additional dose was found to have an additional effect (lines 7, 2, 3; 10, 11, 12; 14, 15, 16).

A fifth treatment was still effective and did not suggest the development of resistance (lines 19 through 24).

Increasing the total dosage with the number of treatments kept constant increased the effect (lines 4, 3; 8, 2; 19, 21, 23).

When total dosage and number of treatments were the same the effectiveness was much greater if some of the treatments were given on the more efficient days of therapy

(days 1, 2, or 3—see Fig. 2) (lines 4, 5; 15, 17).

Divided doses were generally as effective as the same total dose given at one time (lines 1, 2, 4; 7, 8). However, when some of the doses were given on highly efficient days of therapy, the effectiveness was superior to that obtained by giving a single large dose (lines 1, 5, 6).

About midway in these experiments a spontaneous change apparently occurred in the S-91 tumor and results from then on were consistently poorer than previously. (Our stock line of tumor had never been exposed to ThioTEPA.) For the first time large numbers of extremely small spots were noted even in the lungs of those animals treated with the highest dose of drug. Most of these spots were visible only under two-power magnification and a strong light, and many appeared irregular in shape, rather than round. Observation of similarly treated animals for 4 months revealed no change in the number or size of these spots. They were unaffected by further treatment. Microscopic sections revealed clusters of melanin consistent in size with the macroscopically visible spots. In many cases no cellular detail was visible (Fig. 3), and where cell outlines were apparent, the cells were distorted and occurred singly or in small groups. Occasional bizarre giant cells were seen (Fig. 4). No such distorted cells or islands of melanin were seen in sections of untreated lungs (Fig. 5). Because of the dubious viability of these spots for the reasons stated they have been disregarded in presenting the results of this article. If only the larger, growing tumors are counted, the results are comparable to those of the earlier experiments.

When similar experiments were done with other tumors the response to ThioTEPA varied. Thus, ThioTEPA was just slightly less effective in preventing metastases from S-37 when given promptly than it was in preventing metastases from S-91 (Table V). Therapy administered at 48 hours was less effective than immediate therapy which is in contradistinction to the results with S-91.

TABLE II.—TREATMENT OF ARTIFICIAL S-91 METASTASES WITH ThioTEPA

Dose μgm./gm.	*No. of experiments*	*Per cent effective*	*Treated takes**
1	4	1.0 ± 0.9†	34/34
2	5	16.4 ± 10.0‡	44/44
3	6	35.1 ± 2.4	57/58
5	3	88.8 ± 2.2	23/24
10	8	95.4 ± 1.1	79/90
15	3	98.4 ± 0.6	15/24
20	2	99.8 ± 0.1	5/13

ThioTEPA was given intraperitoneally within 3 hours after intravenous injection of tumor cells.
*Animals with some lung tumors/total number of treated animals. (Control animals all had tumor.)
†Standard error of the mean.
‡One grossly abnormal value caused this great deviation.

Walker carcinosarcoma pulmonary metastases in rats did not appear to be affected by ThioTEPA in two different experiments although the drug was given at maximum tolerated dosage (Table VI).

ThioTEPA appeared to be only slightly effective against V2 rabbit carcinoma lung metastases at maximum tolerated dosage (Table VII). In experiment A the results show a significant difference between groups ("p" between 1 and 2 per cent). In the other, the difference, although in the same direction does not reach the 5 per cent confidence level.

DISCUSSION

Systemic ThioTEPA enormously reduces the number of artificial pulmonary metastases from S-91 melanoma. This fact has been demonstrated by using an experimental system which allows for greater precision than is possible with the usual method of "takes and no-takes." The quantitation which can be attained can be seen by comparing the last two columns in Tables I and II. Fine gradations of effectiveness can

TABLE III.—EFFECT OF PRETREATMENT WITH ThioTEPA BEFORE INTRAVENOUS INOCULATION WITH S-91

Time of pretreatment	*Percentage effectiveness*		
	5 μgm./gm.	*10 μgm./gm.*	*15 μgm./gm.*
6 minutes	—	92.0	—
15 minutes	—	91.0	—
30 minutes	—	95.5	—
1 hour	54.0	86.0	73.0
2 hours	0	0	40.0

TABLE IV.—EFFECTIVENESS OF MULTIPLE TREATMENTS WITH Thiotepa

Line	Regimen: Individual doses μg/gm	Regimen: Days given*	Total dose μgm/gm	Av. No. tumors per mouse	Per cent effective
			EXPERIMENT A		
1.....	10	0	10	5.1 ± 1.7†	98.0
2.....	5, 5	0, 5	10	2.8 ± 1.8	99.0
3.....	5, 5, 5	0, 5, 10	15	0.6 ± 0.3	99.7
4.....	3⅓, 3⅓, 3⅓	0, 5, 10	10	3.9 ± 2.0	98.5
5.....	3⅓, 3⅓, 3⅓	0, 2, 4	10	0.7 ± 0.3	99.7
6.....	2½, 2½, 2½, 2½	0, 1, 2, 3	10	0.6 ± 0.1	99.8
7.....	5	0	5	28.0 ± 7.0	88.7
8.....	2½, 2½	0, 5	5	23.0 ± 7.4	92.0
9.....	Control	—	—	212 ± 21.0	—
			EXPERIMENT B		
10.....	3	0	3	182 ± 19.0	40.0
11.....	3, 3	0, 1	6	23.0 ± 6.0	91.0
12.....	3, 3, 3	0, 1, 2	9	2.4 ± 1.0	99.1
13.....	Control	—	—	257 ± 21.0	—
			EXPERIMENT C		
14.....	3	0	3	94.0 ± 15.0	31.0
15.....	3, 3	0, 1	6	31.0 ± 6.5	77.0
16.....	3, 3, 3	0, 1, 2	9	16.0 ± 4.6	88.0
17.....	3, 3	0, 5	6	72.0 ± 16.0	52.0
18.....	Control	—	—	137 ± 22.0	—
			EXPERIMENT D		
19.....	1, 1, 1, 1	0, 1, 2, 3	4	284 ± 36.0	54.0
20.....	1, 1, 1, 1, 20	0, 1, 2, 3, 4	24	2.4 ± 0.8	99.6
21.....	3, 3, 3, 3	0, 1, 2, 3	12	22.0 ± 3.2	96.4
22.....	3, 3, 3, 3, 20	0, 1, 2, 3, 4	32	1.1 ± 0.5	99.8
23.....	5, 5, 5, 5	0, 1, 2, 3	20	4.0 ± 0.9	99.4
24.....	5, 5, 5, 5, 20	0, 1, 2, 3, 4	40	1.0 ± 0.9	99.8
25.....	Controls	—	—	616 ± 57.0	—

*Days after tumor inoculation (day 0 is day of inoculation).
†Standard error of the mean.

be detected by this technique so that the relative efficacy of different dosages and treatment regimens can be evaluated. In order to make possible the detailed quantitative comparisons of this study, a heavy amount of inoculum was given such that the untreated animals would develop hundreds of tumors. This is an artificial situation. A much greater number of complete cures could have been achieved if a more dilute inoculum had been used. A 90 per cent effective treatment would be expected to cure completely 9 of 10 animals with solitary metastases and 50 per cent of animals with 5 metastases.

TABLE V.—EFFECT OF Thiotepa ON ARTIFICIAL S-37 PULMONARY METASTASES

Time of treatment, hours after inoculation	No. of mice	Average No. of tumors	Per cent effective
1½	9	45.6 ± 14.6*	82
3	9	35.9 ± 9.0	86
6	8	25.9 ± 6.2	90
24	9	169 ± 37	66
48	10	114 ± 42	44
72	9	123 ± 29	48
Controls	19	258 ± 34	—

Dose of Thiotepa—10 μgm./gm.; 25,000 cells injected.
*Standard error of the mean.

When treatment is delayed, effectiveness increases and then decreases in a systematic fashion (Fig. 2). Two days' delay in therapy enhances the effectiveness of the drug, and treatment after 4 days' delay is as effective as immediate treatment. Possibly, increased effectiveness with delay up to 48 hours may be caused by an alteration in the metabolism of the cells as they become established. No such increased effectiveness at 48 hours was noted with S-37 tumor. However, this is a rapidly growing tumor and the possibility that such an effect occurred earlier than 24 hours after inoculation has not been excluded and is, in fact, suggested by our data.

The systematic decrease in effectiveness with time after the 48 hour peak is of interest. This appears to be a validation of the assumption that treatment of metastatic implants shortly after surgery would have more chance of success than treatment of older, well established gross metastases.

Failure of ThioTEPA to cause regression of a large human tumor would not preclude the possibility of its being effective against a recent microscopic metastasis.

The experiments using Walker carcinosarcoma lung metastases fail to parallel those of McDonald and associates who showed ThioTEPA given intraperitoneally to be quite effective in decreasing the number of liver takes in rats receiving intraportal injections of this tumor. We found ThioTEPA ineffective in preventing lung metastases from this tumor even though the dose used was 2½ times as large as that used by McDonald and the number of cells injected roughly the same. This discrepancy might be explained by the different site of metastasis. Another possibility is a difference in the strains of Walker tumor used in the two laboratories.

ThioTEPA must exert its antitumor effect either by a direct effect on the cells or by altering the host physiology. If the latter is the case, one would not expect pretreatment to lose its effectiveness so rapidly (Table II). However, this would be expected if the effect were a direct one on the tumor cells and thus dependent on adequate blood levels of the chemical. Supporting this interpretation is the observation that ThioTEPA is tumorcidal in vitro. It is suggested that pretreatment experiments such as these have potential application to the bioassay of ThioTEPA blood levels in experimental animals.

The finding of tumor giant cells and isolated foci of 1 or 2 damaged cells in the lungs of treated animals is of interest. Puck reports that irradiated HeLa cells (tumor cells isolated from a patient with carcinoma of the cervix and maintained in tissue culture) frequently multiply several times and then remain constant in size or degenerate. These are considered to be nonviable cells. Associated with these are giant cells which metabolize rapidly and grow to huge size although they have lost their ability to reproduce. These irradiated cells may be analogous to the ThioTEPA-treated cells which have been described in the foregoing.

TABLE VI.—EFFECT OF ThioTEPA ON ARTIFICIAL WALKER CARCINOSARCOMA LUNG METASTASES IN RATS

	Experiment A—250,000 cells injected			*Experiment B—150,000 cells injected*		
*Day of treatment**	*No. rats*	*Av. No. tumors*	*Per cent effective*	*No. rats*	*Av. No. tumors*	*Per cent effective*
0	9	368 ± 154†	14	11	329 ± 81†	8
1	9	427 ± 54	0	—	— —	—
2	9	395 ± 90	8	11	427 ± 72	−20
Controls	10	428 ± 109	—	12	357 ± 75	—

Dose of ThioTEPA—5 μgm./gm.
*Days after tumor inoculation.
†Standard error of the mean.

It is possible to make some generalizations about treatment schedules with ThioTEPA against mouse melanoma. The highest tolerated total dose of ThioTEPA given in split doses on days 1, 2, and 3 after inoculation is an exceedingly effective form of therapy. There is definite superiority of this regimen over a single large treatment on the day of inoculation. Subsequent repeated doses after the initial course of therapy would be of additional value. Continuation of therapy beyond 3 weeks would not be expected to increase the effectiveness.

A similar formulation for humans would be desirable. Present regimens for clinical therapy with ThioTEPA usually involve treatment with an initial large dose divided into smaller daily components to decrease toxicity, and then subsequent smaller treatments spaced in time to allow for recovery from marrow depression. This treatment schedule is largely empiric and determined more by considerations of toxicity than by its efficiency against tumors. The reason that a more rational program is not possible at the present time is that we lack the kind

TABLE VII.—EFFECT OF ThioTEPA ON ARTIFICIAL V_2 CARCINOMA LUNG METASTASES IN RABBITS

	Experiment A—1,500,000 cells injected			*Experiment B—1,600,000 cells injected*		
*Day of treatment**	*No. of rabbits*	*Av. No. tumors sample lobe*	*Per cent effective*	*No. of rabbits*	*Av. No. tumors sample lobe*	*Per cent effective*
0	3	125 ± 7†	34	7	67 ± 12	21
2	—	— -	—	6	60 ± 12	29
Controls	3	191 ± 5	—	7	85 ± 12	—

Dose of ThioTEPA—5 μgm./gm.
*Days after tumor inoculation.
†Standard error of the mean.

of detailed information in humans that can be obtained in mice. The lack of such information about human tumors is underlined by the following considerations:

1. Different tumors have different susceptibilities to THIOTEPA. In 4 different tumor systems, 2 were highly, 1 slightly, and 1 not at all affected by THIOTEPA. We do not know what proportion of human tumors might be susceptible to THIOTEPA within the permissible dosage range. Certainly considerable caution must be employed in translating the results of animal experiments to the human situation when even among small animals the results vary so strikingly. It is hoped that in the spectrum of human tumors, as in the spectrum of animal tumors, there will be a certain percentage of patients whose tumors are susceptible and who may be spared metastases. This hope is supported by the published reports of reduction in size of some large tumors treated with THIOTEPA.

2. Sensitivity of experimental metastases to THIOTEPA varies systematically with time. If it were known that human tumors followed a similar pattern we could adjust the treatment schedule to take advantage of the maximum point on the curve in Figure 2. Since this is not known and since the 2 mouse tumors studied differed in their day of maximum sensitivity, there is a risk of missing the effective day of therapy by delaying treatment beyond the day of surgery.

3. Dividing a dose may give different results from giving the dose all at one time. Giving the dose in smaller components on successive days would have the advantage of reducing the toxicity so as to permit somewhat larger total doses. Our animal studies suggest that it might also be inherently more efficient. There is a theoretic possibility, however, that if the maximum permissible dose were only moderately effective in humans, dividing this dose into smaller components might leave individual doses which were completely ineffective. The total effectiveness of treatment might thus be seriously compromised.

SUMMARY

1. Systemic THIOTEPA given shortly after the intravenous administration of S-91 melanoma tumor cells is highly effective in reducing the number of subsequent lung metastases in mice.

2. Delay in therapy of 1 or 2 days increases the effectiveness of such treatment. Further delay in therapy results in a gradual falling off of effectiveness.

3. Under certain conditions, the administration of the drug in divided doses over several days may significantly improve the efficiency of therapy.

4. THIOTEPA differs qualitatively and quantitatively in its effectiveness against different tumors in different animals. Hence estimates of its effectiveness against human tumors must be made with very great caution.

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THE INDICATIONS FOR BLOOD VOLUME DETERMINATIONS IN MAJOR SURGICAL PROCEDURES

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DURING THE PAST SEVERAL YEARS the subject of blood volume has received considerable recognition in the clinical as well as the basic science literature. Unlike many subjects whose frequent discussion outweighs their clinical import, the subject of blood volume, although known to all, remains far from saturated from the standpoints of clinical emphasis and utilization. Many clinicians contend, however, that they find adequate, without personal investigation, the usual indices of blood replacement (hemoglobin, hematocrit, and erythrocyte count). Others believe that although these indices are not entirely satisfactory, the time, effort, magnitude, and expense incident to measurement of blood volume preclude its use. Investigation of this problem will occasionally yield results that conflict with some of the conclusions drawn from previous studies on the subject. This report is intended to show why the subject of blood volume is worthy of further treatment, to emphasize further some previously described observations, and to stress the occasional need for transfusion of the separate blood components rather than whole blood.

MATERIALS AND METHODS

The present study is based upon results obtained from 100 patients admitted to the surgical service of the Vicksburg Hospital. A large percentage of this group included members of a low economic class. All were suffering from lesions of considerable magnitude.

From the Surgical Service of the Vicksburg Hospital, Vicksburg, Mississippi, and the Department of Surgery, University of Mississippi School of Medicine, Jackson, Mississippi.

The following determinations were made: (1) hemoglobin, in grams per 100 milliliters, (2) red blood cells, in millions per cubic millimeter, (3) hematocrit, in per cent, (4) plasma volume, obtained by the Evans blue method on the basis of present weight, optimal weight, and determined values, and (5) blood volume on the same basis. These values were determined on three different occasions: (1) after admission to the surgical service, (2) 24 hours postoperatively, existing deficits having been corrected preoperatively, and (3) 7 days postoperatively. The patient's optimal preillness weight was used as the basis for computing the deficit.

The accuracy of the Evans blue method has been under discussion since its origin. With the advent of radioactive materials, further questions have been raised about the T-1824 method. The procedure, properly done, has a reputed error of 3 per cent according to Gregersen and has been assigned a generous margin of error of 10 per cent by others. As conducted in our laboratory, it is safely within this 10 per cent margin. It seems paradoxic that such a small margin of error in blood volume should precipitate such a controversy when the accuracy of red blood cells, hemoglobin, and hematocrit have gone without serious question for so many years.

RESULTS

In Figure 1 are shown the values of plasma volume, blood volume, hematocrit, red blood cells, and hemoglobin obtained on admission for the 100 patients in this series. It is readily apparent that for about two-

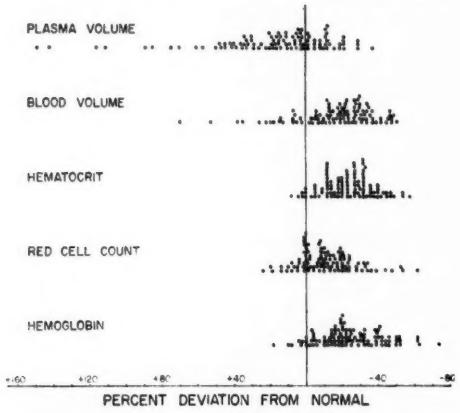

FIG. 1. Preoperative hematologic values in 100 surgical patients, expressed as percentage deviation from normal.

thirds of the patients the values for plasma volume were increased above normal, one-third from zero and +20 per cent and one-third from +20 per cent and an astonishing +150 per cent. On the other hand, only about one-fifth of all the patients had increased values for blood volume; 70 of the remaining patients had values that fell between −20 and −40 per cent and 10 had values that approached −50 per cent.

Of the three procedures usually employed in determining vascular content (hemoglobin, hematocrit, and red blood cells), it would appear from Figure 1 that the hematocrit more accurately reflects the blood volume than the remaining two determinations; the fallacy of this observation will be shown later. The red blood cell count particularly, and the hemoglobin to a lesser extent, are grouped more toward normal, although practically all patients showed impressive deficits. Thus, Figure 1 shows that plasma volume was usually above normal, frequently strikingly so, that 80 of 100 patients demonstrated blood volume deficits ranging from −2 to −51 per cent, that the hematocrit would appear to reflect blood volume, that deficits of hematocrit, hemoglobin, and red blood cell count were the rule, the erythrocyte count being normal oftener than the other two values.

Figure 2 shows the values obtained on the first postoperative day. It will be remembered that preoperative deficits were corrected, hemoglobin, hematocrit, and red blood cells being used as criteria except in a few cases, and that operative blood loss was replaced as accurately as possible on the basis of the operating team's impression of blood loss. The plasma and blood volumes on the day after operation were similar to those obtained preoperatively. The deficits in hemoglobin, hematocrit, and red blood cell count, although still evident, seemed to be grouped more toward normal, with no values below −40 per cent. Figure 3 shows the values obtained 1 week postoperatively, which are essentially similar to those obtained on the first postoperative day.

Table I presents the means and standard deviations of the various determinations obtained on the three occasions. Analysis of these data yielded no statistically significant difference between the values for any of the three determinations. Table II shows the results of the mathematical analysis of the difference between the blood volume and the hemoglobin, hematocrit, and red blood cells. No correlation exists between blood volume and any of these three measurements.

TABLE I.—MEANS AND STANDARD DEVIATIONS OF VARIOUS DETERMINATIONS

	Mean total blood volume, ml.	*Mean total plasma volume, ml.*	*Mean hematocrit, per cent*	*Mean hemoglobin, grams per cent*	*Mean red blood cells X10⁶*
Group I (preoperative)	5022 ±1503	3248 ± 747	35.0 ± 4.0	13.32 ± 2.89	4.44 ±0.83
Group II (1 day postop.)	4990 ±1615	3060 ±1201	39.0 ± 1.8	15.3 ± 1.98	5.05 ±0.51
Group III (1 week postop.)	5144 ±1317	3248 ± 926	37.0 ± 5.2	14.28 ± 2.88	4.80 ±1.26

In Figure 4 are shown the values on admission for each determination in each of the 100 patients. The values for hemoglobin, which was considered the most frequently used index of blood replacement, are arranged in descending order. Corresponding values for red blood cell count, hematocrit, blood volume, and plasma volume are also shown. The red blood cell count and hematocrit roughly parallel the values for hemoglobin. Even more striking is the lack of any parallelism between the values for blood volume or plasma volume and those for hemoglobin, red blood cell count, and hematocrit.

Figures 5, 6, and 7, which contain the values on admission for 9 different patients (3 in each illustration), demonstrate the fallacy of estimating blood volume from hemoglobin, hematocrit, and red blood cell count. Various investigators have questioned the propriety of using the patient's optimal weight as a gauge for deficits. These figures demonstrate that no matter which weight, optimal or existing, is used, the differential remains between the values for hemoglobin, hematocrit, and red blood cell count and those for blood volume and plasma volume.

In Figure 5, notice the similarity between the hematocrit, red blood cell count and hemoglobin in patients 1 and 2 but the opposite direction of the values for blood volume and plasma volume. In patients 2 and 3, the values for blood volume and, to a lesser extent, the deviations of plasma volume are in the same direction, whereas those for hemoglobin, hematocrit, and red blood cell count are in the opposite direction. Figure 6 demonstrates the same pattern: similar values for hematocrit, red blood cell count, and hemoglobin in patients 4 and 5, with pronounced differences in plasma volume and blood volume. Again, values for plasma volume and blood volume are similar in patients 5 and 6, but values for hemoglobin and red blood cell count are in opposite directions. In Figure 7, the hematocrit, red blood cell count and hemoglobin of patients 7 and 8 are alike, but the blood volume and plasma volume are in

TABLE II.—MATHEMATICAL ANALYSIS OF DIFFERENCE BETWEEN BLOOD VOLUME AND RED BLOOD CELLS, HEMOGLOBIN, AND HEMATOCRIT

Values correlated	*Correlation coefficient*
Red blood cells to blood volume	+0.252
Hemoglobin to blood volume	+0.189
Hematocrit to blood volume	+0.103

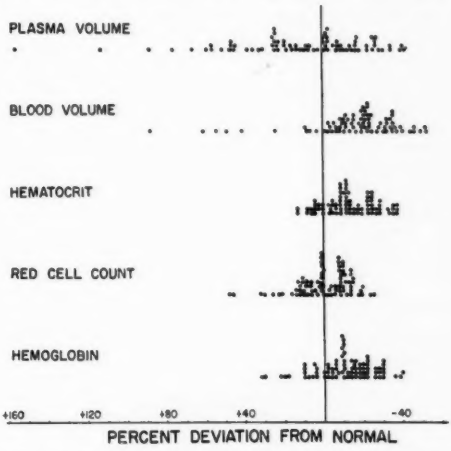

FIG. 2. Hematologic values in 100 surgical patients on the first postoperative day, expressed as percentage deviation from normal.

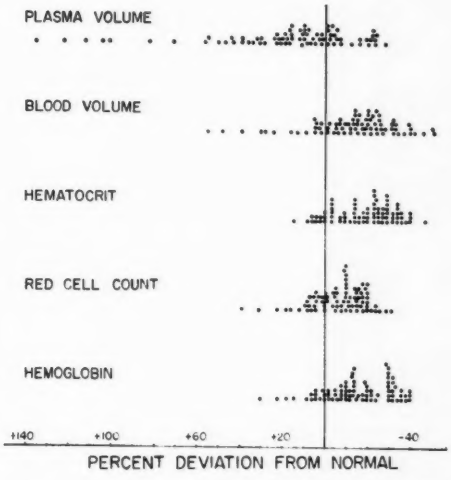

FIG. 3. Hematologic values in 100 surgical patients 1 week postoperatively, expressed as percentage deviation from normal.

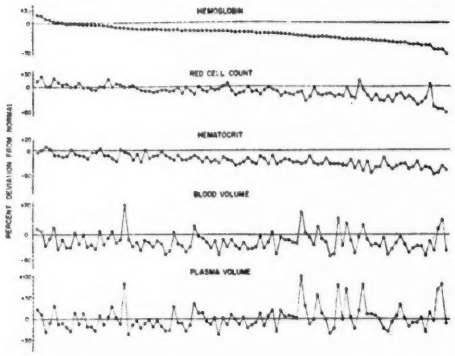

FIG. 4. Hematologic values on admission of 100 surgical patients. Values for hemoglobin have been arranged in descending order. Beneath each hemoglobin determination are charted the corresponding values for erythrocytes, hematocrit, blood volume, and plasma volume.

opposite directions. Blood volume and plasma volume of patients 8 and 9 are alike, but there is a pronounced difference for the values of the hematocrit, red blood cell count, and hemoglobin.

DISCUSSION

Clark and associates have stressed the frequency of decreased blood volume in seriously ill patients who require major operations. The present study supports this observation. Roughly 80 per cent of the patients had blood volumes below normal on admission; one-half had values more than 20 per cent below normal, and one-fourth exhibited deficits in excess of 30 per cent. If the blood volume in this last group of patients were to drop suddenly, moderate to severe clinical shock would ensue. Fortunately, however, this loss occurs insidiously and, as the circulating hemoglobin and red cell mass shrink, the plasma volume expands to compensate for the deficit. Inspection of the figures for plasma volume reveals that only 30 per cent of the values were subnormal, and that most of these were much less than 20 per cent below normal. Plasma volume was increased in the remaining 70 per cent of the patients, one-half of whom had a plasma volume in excess of 20 per cent above normal.

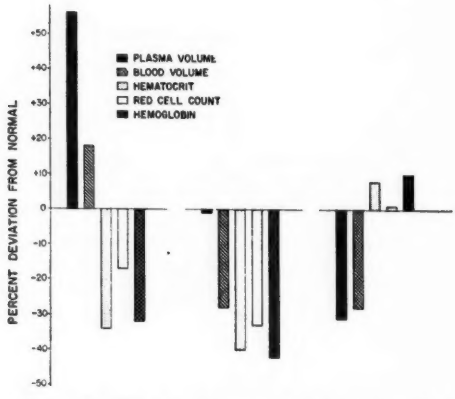

FIG. 5. Hematologic values on admission of 3 surgical patients (Nos. 1, 2, and 3), showing lack of concordancy between values for plasma and blood volumes and those for hematocrit, red cell count, and hemoglobin.

In the past, and even today, the emphasis has been on transfusion of whole blood to make these patients acceptable surgical risks. This study would suggest that there is frequently need for transfusion of red blood cells alone rather than whole blood. Little imagination is required to see what would happen to an elderly person with cardiac disease if he were to receive 1,500 milliliters whole blood when his plasma volume was already 40 per cent in excess of normal. This situation can be detected only by use of blood volume techniques. Only because man is a hearty, quickly adaptable organism have more frequent disasters from this chain of events been prevented.

Admittedly, the use of whole blood will be applicable in the majority of cases, but plasma volume assays are needed for intelligent interpretation of each compartment and for administration of the proper substance (washed blood cells or whole blood). The margin of error is thus significantly reduced in patients who, for inherent pathologic reasons, can ill afford any further expansion of an already loaded intravascular component.

Blood volume determinations have been carried out in large series of patients with

gastric, pulmonary, and pelvic lesions, as well as many other conditions. In many of the resulting publications, emphasis has been placed on the mean deviation of the blood volume from normal, and it has been suggested that a certain average amount of blood is necessary for return of the intravascular status to normal. This practice is commendable, because it furnishes to those who fail to carry out blood volume determinations an estimate of the amount of blood necessary to correct deficiencies. Furthermore, it reflects deficiencies not mirrored in the hemoglobin, hematocrit, and red blood cell count. Basing any conclusions on such means, however, is inadvisable because of lack of correlation between the various values shown in Figure 4. In other studies (3), we have found no correlation between blood volume and a specific disease process, age, sex, loss of weight, or duration of disease. Thus, accurate knowledge of blood volume is derived from individual determinations rather than averages previously determined by others.

Comparison of Figures 1 and 3 shows that the blood volume on admission did not differ greatly from that existing 1 week postoperatively. Although deficits had been corrected and blood loss had been replaced at operation, frequent large deficits still existed. Our criteria for postoperative transfusions are essentially the same as those used in other institutions. Because the urgent need for blood is considered passed, because blood transfusion carries a certain risk, and because blood itself is not especially plentiful, transfusion is not given unless specifically demanded by bleeding, by an exceptionally low count, or by other emergencies. The consequences could be catastrophic should an abrupt complication, such as hemorrhage or evisceration, occur in these patients with greatly reduced blood volumes. A large percentage of the patients would probably fare better, and an occasional fatality might be prevented if this frequent postoperative deficit were corrected. Along this line it is interesting to recall the many references to

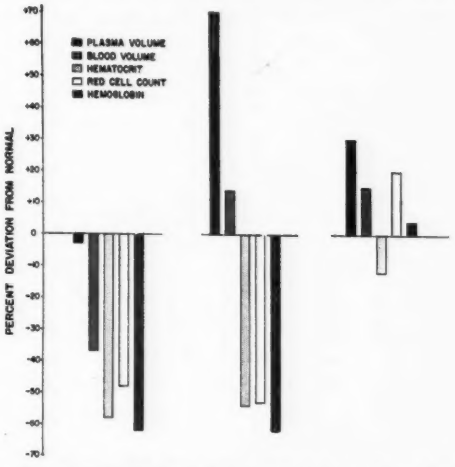

FIG. 6. Hematologic values on admission of 3 surgical patients (Nos. 4, 5, and 6), showing the same type of variations as in Figure 5.

the increased incidence of thrombophlebitis and phlebothrombosis in patients with anemia.

Finally, we would stress once again the fallacy of attempting to estimate intravascular content from the usually employed determinations of hemoglobin, hematocrit, and red blood cell count. Table II proves statistically, and Figures 5, 6, and 7 offer convincing visual evidence, that the hemo-

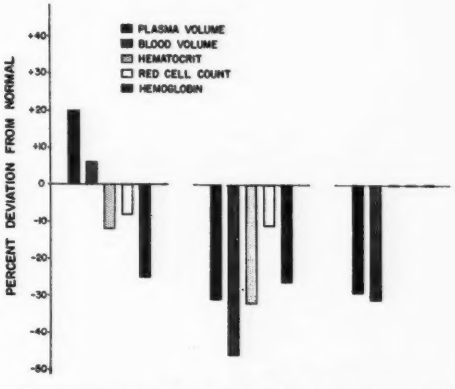

FIG. 7. Hematologic values on admission of 3 surgical patients (Nos. 7, 8, and 9), showing the same type of variations as in Figure 5.

globin, hematocrit, and red blood cell count do not accurately reflect blood volume. Obviously, every patient does not need a blood volume determination before operation any more than a patient with an ingrown toenail needs a battery of liver function tests. However, when the patient is elderly or extremely young and the allowable margin of error is narrowed, the true status of his blood volume can be determined only by such measurements. The reason such determinations are not obtained in most hospitals probably resides in the fact that the physician remains unconvinced of their necessity or even advantage over the usual hemoglobin, hematocrit, and red blood cell determinations. The frequent excuse that the determination is difficult, time-consuming, and demanding of extra skill is not at all valid when this procedure is compared with other more complicated, but commonly employed, laboratory procedures. We contend that blood volume determinations can be done with little or no change in the routine operation of the laboratory and with significant benefit to the surgical patient.

SUMMARY

1. Plasma volume measured by the Evans blue dye method, blood volume, hemoglobin, hematocrit, and erythrocyte count were determined in 100 surgical patients on admission, on the first postoperative day, and 7 days postoperatively.

2. Values for plasma volume on admission ranged from +20 to +150 per cent in two-thirds of the patients.

3. Values for blood volume on admission were below normal in four-fifths of the patients, ranging from −2 to −50 per cent.

4. Large deficits in hemoglobin, hematocrit, and erythrocytes were found to exist on admission.

5. No statistical differences existed between the values on admission and those obtained on the first and seventh postoperative days despite correction of deficits and replacements of operative blood loss.

6. No correlation was demonstrable between the values for blood volume or plasma volume and those for hematocrit, hemoglobin, and erythrocyte count.

7. Blood volume and plasma volume measurements indicate a frequent need for the transfusion of red blood cells alone rather than whole blood.

8. Because of the unpredictability of blood volume and plasma volume, replacement needs in a specific situation should not be based on mean values.

9. Postoperative complications and fatalities might be reduced if postoperative blood volume deficits were recognized and corrected.

10. It is suggested that the adoption of routine blood volume determinations in hospital laboratories is not so formidable a procedure as is generally imagined.

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SOME ASPECTS OF WATER AND ELECTROLYTE EXCRETION

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I PROPOSE TO DEAL with the particular problem of the facultative excretion of water and its mode of control, i.e., the processes that underlie the diuresis response of the living mammal to the ingestion of water, and along with this the related problem of contemporary electrolyte excretion. The subject is one in which I became interested some 30 years ago when the late Professor Starling and I showed that the dog's kidney perfused in the isolated state secreted a profuse and watery urine, and that this diuresis was inhibited by the addition of postpituitary extract to the perfusing blood, the inhibition being accompanied by an increase both in the concentration of chloride in the urine and in the rate of chloride excretion. We suggested at that time that some substance or substances with an action similar to that of postpituitary extract were normally present in the intact mammal and served as the means through which the kidney was controlled in its important function of regulating the output of water and of chloride. Fortunately, the ostensibly simple phenomenon of water diuresis is one that appears, at least in a form susceptible to quantitative analysis, only when the animal is in living correspondence with its external and internal environments and unbenumbed by that state of anesthesia which, in ministering to technique, frustrates or embarrasses interpretation.

RELATION OF ABSORPTION TO EXCRETION OF WATER

Under controlled conditions the diuretic responses of a normal bitch to a fixed dose of water are fairly uniform; and one of the earliest findings in the analysis of the response, and one that clearly showed that the phenomenon was less simple than it at first sight appeared to be, was the fact that the course of the absorption of water from the gut was well in advance of that of the excretion of water by the kidney. In one series of animals the peak of the water load curve, i.e., of the course of the volume of water that had been absorbed from the gut but not yet excreted by the kidney, preceded the peak rate of urine flow by 15 minutes. If then, as is reasonable, we regard the water load curve as tracing the intensity of the stimulus to which the kidney is ultimately responding, we must conclude that there is a definite time lag between the maximum intensity of stimulus and the maximum response by the kidney.

INHIBITION OF ESTABLISHED DIURESIS BY EMOTIONAL STRESS

Now this diuresis response may, after its establishment, be inhibited by various agencies. It had been known for many years that exercise and emotional factors may produce a decrease in urine flow; and this decrease had been implicitly or explicitly attributed to a vasomotor source. Such inhibitory response to emotional stress may be readily obtained by carrying a weak faradic current to the subcutaneous tissues through surgically clean needle electrodes, and increasing its strength until the animal shows signs of resentment. In 1938 Rydin and I undertook experiments to determine the essential cause of the resultant fall in the rate of water excretion by the kidney.

Mechanism of the inhibition. Serial operations comprising (a) division of the renal nerves, (b) removal of the right suprarenal

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gland and denervation of the left, and (c) decentralization of the whole abdominal sympathetic system with removal of ganglia, from the first lumbar to first sacral inclusive, were found, by tests before and after each surgical procedure, to produce no essential change in the course of the inhibitory response to emotional stress. Moreover, records of the arterial blood pressure (obtained from the femoral artery under local anesthesia) during these inhibitory responses showed that after denervation of the kidneys and after subsequent removal of the right suprarenal and denervation of the left, the pressure rose during the emotional stress,while after removal of the abdominal sympathetic chains the pressure remained unaffected by such stress. The inhibition, therefore, was independent of the renal nerves and of the endogenous release of adrenaline; and from the blood pressure records it was apparently independent, too, of any contemporary change in renal blood flow. The view that the humoral agent released by the stress and directly responsible for the inhibition of urine flow was postpituitary antidiuretic substance was supported by the minuteness of the minimal effective dose of this substance, by the presence of a suitable structural basis for the emotional release in the innervation of the pars nervosa of the pituitary by fibers from the supraoptic and paraventricular groups of hypothalamic nuclei, and by the similarity both in lag of onset and in external form between the inhibitory responses to intravenously administered postpituitary extract and those to emotional stress, the responses becoming, with a suitable dose of extract, indistinguishable. Furthermore, the antidiuretic action of the extract is unaffected by denervation of the kidneys, and is unaccompanied by any appreciable change in renal blood flow.

One felt confident, therefore, that removal of the posterior lobe in the dog would be followed by a big diminution in the inhibitory response to emotional stress. This, O'Connor and I found to be so. Comparison of the postpituitary extract equivalent of the emotional inhibition before with that after removal of the posterior lobe showed that only about 5 per cent of the antidiuretic function of the neurohypophysis, as expressed in the inhibition by emotional stress, remained when the posterior lobe had been removed.

These observations, coupled with the fact that the release of postpituitary antidiuretic substance may be caused by such mild disturbance of the central nervous system as comes within a physiologic range—even the anticipation of a nocuous stimulus which the animal has previously experienced may be effective—encouraged an attempt to determine whether the secretion of this substance were not continuously varying with, and under the direct control of, some factor in the animal's internal environment, to the maintenance of which factor within a narrow physiologic range the renal secretion of water and of chloride would specifically contribute. Such factor is clearly the osmotic pressure of the arterial blood. A fall in this osmotic pressure will inevitably accompany the increased water load of the animal after water administration. Such fall was demonstrated by Baldes and Smirk in 1934; and, indeed, as long ago as 1916 Haldane and Priestley postulated that in water diuresis the kidney was responding directly to an increase in the ratio of water molecules to total molecules in the plasma—the "diffusion-pressure of water"—and they drew an analogy between such sensitiveness of the kidney to the pressure of water molecules in the plasma and that of the respiratory center to the partial pressure of carbon dioxide. In view of the more recent work, however, it seemed more likely that a change in osmotic pressure—if, indeed, this were the primarily effective factor in the sequence of underlying events—would be operating through the intermediation of the neurohypophysis, and it thus became of interest and importance to put such hypothesis to the test of experiment. As we shall see, the determining osmotic pressure of the plasma is not the total pressure as conceived physically and as

measured in vitro, but derives from the specific permeability of a living membrane with respect to each of the plasma solutes to which it is exposed.

OSMOTIC RELEASE OF ANTIDIURETIC HORMONE

For these experiments (12) healthy bitches were perineotomized in order to make catheterization of the bladder simple and undisturbing, and after healing was complete a Van Leersum "carotid loop" was made on one side, followed after a suitable interval by the formation of a similar loop on the other side. These loops provided a means by which the injection or infusion of a chosen solution could be made directly and painlessly into the common carotid blood during an established water diuresis in the living animal. Preliminary observations showed that the intracarotid injection of isotonic solutions and the intravenous injection of hypertonic solutions (e.g., ⅓ molar sodium chloride) produced no immediate effects on the course of urine flow. When, however, hypertonic solutions of sodium chloride were injected into the carotid, definite inhibitory responses were observed. The magnitude of the responses varied with the tonicity of the solution at constant rate and period of injection, and with the period of the injection at constant volume and tonicity of solution. Moreover, the character of the inhibitory responses simulated so closely the known character of the response to the intravenous injection of postpituitary extract that it appeared highly probable that they were of pituitary origin. This theory was put to the test of experiment, and it was found that after removal of the posterior lobe the response to a given intracarotid injection of hypertonic sodium chloride was very much reduced in size. It is, therefore, a valid procedure to assay the responses in terms of postpituitary extract; and when this is done it is found that the response to a given intracarotid injection is diminished by some 90 per cent as the result of removal of the posterior lobe.

It now became important to know whether the sodium chloride was acting specifically in eliciting the responses to intracarotid injections, or by virtue of the increase which it produced in the osmotic pressure of the plasma. To this end comparison was made between the effects of equal increases in the osmotic pressure of the carotid blood produced by injections of sodium chloride, sodium sulfate, sucrose, dextrose, urea, and ethanol. The local increase in the osmotic pressure of the carotid blood was of the order of 50 to 100 per cent, and the injections were made at uniform speed over periods of 10 to 20 seconds. While the responses to sodium chloride, sodium sulfate, and sucrose were indistinguishable, the response to dextrose was a little smaller, and urea and ethanol were found to be quite inactive. Seeing that the only common and equal change in property of the carotid blood caused by the injection of the sodium chloride and sucrose solutions is the increase in osmotic pressure, and that both produce quantitatively the same release of postpituitary antidiuretic substance, the osmotic determination of the phenomenon is beyond cavil.

It became justified, therefore, to introduce the term "osmoreceptors" as descriptive of the autonomic receptive elements with which the neurohypophysis is functionally linked, and through whose activation the pituitary antidiuretic substance is released. The term was, of course, introduced without prejudice to any specific permeability which the receptors might be shown to exhibit to their molecular environment; and the facts so far presented show that when they are exposed to short-lived and relatively large increases in the osmotic pressure of their environment, their "membrane" is relatively impermeable to sodium chloride, sodium sulfate, and sucrose, less impermeable to dextrose, but freely permeable to urea and ethanol.

It then became of interest to determine the effects of exposure of the receptors to much smaller increases in osmotic pressure but maintained over longer periods. For

this purpose, intravascular infusions of various solutes were made at uniform rates over periods of 10 and 40 minutes; and it is with some of the results of the 40 minute infusions that I propose now briefly to deal.

When, during an established water diuresis, sucrose is infused into a common carotid artery for a period of 40 minutes and at such a rate that the calculated local increase in osmotic pressure is a little less than 2 per cent, the urine flow after a latent period of some 5 minutes begins to fall, and continues to do so until the flow is some 10 per cent of the original rate. After the infusion is stopped the urine flow begins to increase again. The same infusion, but given intravenously, has no such antidiuretic action. But when to such intravenous infusion postpituitary extract is added in such amount that some 1.2 micro-units are entering the circulation each second, there is an inhibition of urine flow the course of which follows closely that produced by the intracarotid infusion of sucrose alone. When comparable experiments are made with sodium chloride the results are very similar to those with sucrose, the response to a maintained local increase of 1.8 per cent in the osmotic pressure of the blood in one common carotid having a postpituitary extract equivalence of 1 micro-unit per second, which is very close to the value reported just now for sucrose.

Physiologic significance of the release. Three conclusions follow from the results of the 40 minute infusions: First, increases in the osmotic pressure of the arterial blood are still operative in releasing postpituitary antidiuretic substance when they are reduced to values well within a physiologic range. Secondly, the results demonstrate that this small induced change in the osmotic pressure of the arterial blood—a change which evokes a reduction in urine flow to some 10 per cent of the maximum rate of which the kidney is capable during water diuresis—itself causes the release of postpituitary antidiuretic substance at an average rate of 1 micro-unit per second, this being the intermediating agency through which the change in osmotic pressure becomes effective. The third conclusion from the results of the 40 minute infusions is that, with the recovery of urine flow when the intracarotid infusion is stopped, the secretion of postpituitary antidiuretic substance is now being inhibited by the local fall in osmotic pressure and consequent depression of activity in the osmoreceptors, the progression of this recovery being attributable solely, I imagine, to the gradual disappearance of the quantity of antidiuretic substance that was maintaining the secretion of urine at a nondiuretic level. The absorption of water from the gut was complete long before and could not, as in the initial diuresis, be affecting the course of this secondary diuresis. The latent period between the peak of the water load curve and the maximum rate of urine secretion, to which I referred earlier, is clearly to be attributed to the same process. Moreover, while the primary diuresis is preceded and accompanied by a small increase in renal plasma and filtrate flows, the degree of increase varying with the water load as shown by Sellwood and Verney, the secondary diuresis appears while the water load is decreasing, and any drift in the plasma and filtrate flows will then be in the direction of a fall. Nevertheless, water diuresis is, of course, dependent upon an adequate primordial supply of glomerular fluid. Failure to realize this has, I think, been the cause of the many assaults to which the neurohypophysial theory of water diuresis, and indeed of diabetes insipidus, has been subjected during its checkered career, from experimental work in which factors of qualitative or quantitative abnormality have undesignedly obtruded as accompaniments of technical procedures. The work that I have put before you on the living animal shows, I believe, that neurohypophysial function is, under normal circumstances, an essential component of the processes involved in the renal response to ingested water, and that the antidiuretic secretion of the neurohypophysis is a hormone in the physiologic sense that

TABLE I

	1 nephron			2 kidneys: 10^6 nephrons
Portion of nephron	*Length, mm.*	*No. of cells per mm. length of embedded tubule*	*Total No. of cells*	*Total No. of cells*
Proximal convolution	13.7	740	8,900	8.9×10^9
Thin segment of Henle's loop	5.0	210	920	0.9×10^9
Thick segment of Henle's loop	8.7	590	4,500	4.5×10^9
Distal convolution	5.0	600	2,640	2.6×10^9
Totals	32.4	—	16,960	1.7×10^{10}

The lengths of the component parts of the dog's nephron are taken from the measurements and illustration in the paper by Oliver, Bloom, and MacDowell. The length of a complete proximal convolution which I isolated in a partially macerated dog-kidney was 14.6 millimeters. The number of cells per millimeter length of each portion of the nephron is the average in a series of counts of nucleoli which I have made in 10, 15, and 20 micron sections of paraffin or celloidin embedded material. The figures for total number of cells are corrected for shrinkage of embedded tissue (13)

its liberation is mainly and continually governed by the contemporary concentration of sodium chloride in the arterial plasma. The physiologic fitness of this control is emphasized by its quantitative aspects, in that changes within the range and of the order of 1 per cent in the osmotic pressure of the blood lead, through the intermediation of the antidiuretic hormone, to changes in the rate of water excretion within the range and of the order of 1,000 per cent. The maintenance of near constancy in the osmotic pressure of the internal environment is thereby largely achieved.

The rate of release of antidiuretic hormone in the osmotic suppression of a water diuresis, viz., 1 micro-unit per second, agrees well with the results of Shannon's experiments on replacement therapy in dogs with diabetes insipidus. In such animals Shannon obtained graded antidiuresis with intravenous infusions of 1 to 5 milli-units per hour, and minimal urine flows were usually obtained with the upper limit of this range. My figure of 1 micro-unit per second for the rate of endogenous release at such "resting" rates of urine flow as obtain at the subsidence of water diuresis in the normal dog corresponds with 0.5×10^{-9} grams per second in terms of the standard powder. This quantity, in view of the recent achievement of du Vigneaud and his colleagues in isolating and determining the chemical structure of vasopressin, can now be expressed 2×10^{-12} grams of the pure substance, i.e., of the order of 0.2 micrograms per day. Vasopressin has an octapeptide structure and its molecular weight is about 1,000, there being small species differences in its aminoacid constitution. Now the number of cytons in the supraoptic and paraventricular nuclei of the dog is of the order of 10^5. If, then, all the neurons are contributing to the release of 1 micro-unit per second (i.e., 12×10^8 molecules) at "resting" rates of urine flow, each neuron will be releasing on an average about 12,000 molecules per second. Further, the intravenous injection of 1 milli-unit (i.e., 12×10^{11} molecules) in the dog reduces the urine flow during water diuresis to some 10 per cent of its established value; and as the total number of cells in the renal tubules is of the order of 2×10^{10} (Table I), this dose of hormone will allow a maximum average of 60 molecules per cell, maximum in the sense that all the injected molecules are regarded as contributing to the big antidiuretic response. This number of molecules per cell is far below that needed to produce manifest effects in tissues or in populations of cells by the application of drugs. Such effects need a ratio of tens to thousands of millions of molecules per cell. The very low and maximally effective ratio of vasopressin molecules to kidney cells given (60:1) supports, perhaps, the view that the action of the hormone is restricted to a fraction only of the total length of the tubule endothelium; but even if we assume that all the injected molecules are taken up by and react with the cells of the distal convolution alone the ratio becomes only some 500:1. The volume of a distal tubule cell in the dog is about 1.7×10^3 cubic microns.

LOCALIZATION OF THE OSMORECEPTORS

I come now to the question of the localization of the osmoreceptors. It was early shown that they are not in the carotid sinus nor in the carotid body. Moreover, ligation of the internal carotid near its origin definitely affected the responses to injections of hypertonic solutions into the ipsilateral common carotid trunk, and it was predicted that were the internal carotid tied intradurally, i.e., beyond its anastomotic connection with the internal maxillary branch of the external carotid, the responses to a raised osmotic pressure in the common carotid trunk of the same side would be consistently and permanently suppressed. This, Jewell and I found to be so.

Confirmation of the cephalic localization of the receptors having thus been obtained, we then attempted to discover where, within the substance of the brain, they reside. The test of their activation has been the inhibition of urine flow by intracarotid infusions of hypertonic solutions during established water diuresis. By surgical means the cephalic field of distribution of the carotid arteries has been restricted to defined regions of the brain, and information has thus been acquired on the osmoreceptive status of these regions. In this way it has been contrived that the evidence for the localization of the osmoreceptors should rest solely on the use of a blood-borne physiologic stimulus appropriate to the sensory elements in question. The preliminary needs of the enquiry were, first, an anatomic investigation of the arterial connections of the circle of Willis and of the detailed vascular architecture of the diencephalon and hypophysis; and secondly, the devising of a method to trace the distribution of arterial blood, and the application of this method to the demarcation of the cerebral fields of carotid and vertebral arteries. To trace the distribution of arterial blood two colored suspensions, a black and a blue, have been employed. The particle size of each is some 1 to 2 microns; both suspensions are freely miscible with blood, cause no circulatory disturbance in the living animal during the period of their infusion, tolerate histologic procedures, and are readily differentiated in the capillary beds of serial sections of the celloidin-embedded brain. The suspensions are infused, one into each carotid trunk, at a terminal experiment in which the animal is suddenly killed by the intracardiac injection of chloroform before the suspensions have had time to recirculate. Thus the regions supplied by each carotid can be readily mapped on projection drawings of the serially sectioned brain. Attempts are then made to correlate the distributions so found with any changes that had previously been observed in the osmotic responses to intracarotid infusions as a result of some surgical interference with the cerebral branches and vascular connections of an internal carotid artery. The surgical approach to these has been by the temporosphenoidal route, a route which gives an excellent exposure of the trifurcation of the internal carotid, and through which one or more of its branches may be tied.

In the first place, the naturally occurring asymmetry of the arterial supply to the posterior lobe of the pituitary gland has led to the elimination of this structure as a site of osmoreceptors. The lobe is supplied by a small artery which arises from the internal carotid or the anastomotic artery in the cavernous sinus, and the origin of the vessel may be unilateral or bilateral. In each of a total of 8 animals it was found that the posterior lobe was supplied with blood originating exclusively from one carotid, yet an osmotic release of antidiuretic hormone had been obtained from infusions of hypertonic solutions into the other carotid.

The exclusion of carotid blood from the posterior brain stem has been achieved by (a) the ligation of the two occipital arteries, thus stopping the flow of carotid blood into the vertebral streams via the occipitovertebral anastomoses, and, on one side by (b) the ligation of the occipital and posterior communicating arteries. Osmotic responses to carotid infusions were retained after

these procedures, and thus made secure the assignment of the receptors to the prosencephalon.

Of prosencephalic structures the greater part of the telencephalon has been eliminated from being the receptor site by demonstrating the ipsilateral retention of responses after total hemispherectomy. Furthermore, the heavy degenerative cell loss in all thalamic nuclei of the hemispherectomized animal, excluding some cell groups of the midline, substantiated earlier indications that the receptors were not in the dorsal diencephalon. Alternative and equally compelling evidence for this conclusion was obtained from experiments in which carotid blood was directly excluded from the thalamus. Such exclusion was attained by tying the posterior communicating and occipital arteries of one side together with the middle cerebral or anterior cerebral artery. It was also attained in an experiment in which the left internal carotid was tied intradurally, this resulting in a redistribution of blood from the circle such that the thalamus was supplied entirely from vertebral sources. It was thus deprived of any right carotid blood although osmotic responses to intracarotid infusions on this side were retained.

The collation of the several evidences that I have just summarized led to the inference that the osmoreceptors are situated somewhere in the anterior hypothalamus or preoptic areas. This was the only region of the brain which had invariably been supplied by that carotid from infusions into which osmotic responses had been obtained. An interesting support for the conclusion that the receptors lie in this region of the brain came from an animal in which the right internal carotid was tied intradurally. Before the ligation, big responses were obtained to infusions into the right carotid, and small responses to infusions into the left. After the right internal carotid had been tied the responses to right-sided infusions vanished, but those to left-sided infusions became very much larger. And when, later, the cerebral distributions of the two carotid bloods were determined by the colored suspensions method, it was found that left carotid blood was not only supplying the left anterior hypothalamus but had trespassed across the midline to supply this very region on the right side as well.

Now this osmoreceptive zone, of a volume of about 100 cubic millimeters, is supplied from the internal carotid, the anterior and middle cerebral, and the posterior communicating arteries by tiny branches that arise in the immediate neighborhood of the carotid trifurcation. If, then, these three branches were tied, each some 3 or 4 millimeters from its origin, one would expect osmotic responses to be retained on that side seeing that the osmotic stimulus would be being carried just to that part of the brain where the receptors lie. Two experiments of this nature were made, and in each instance responses to ipsilateral carotid infusions were completely absent after operation. This was a sobering experience, but it was in part allayed by postmortem findings. In the one animal a cyst had appeared in the ipsilateral anterior hypothalamus involving the whole of the dorsal region, and sending a tongue to the floor of the tuber cinereum through the posterior division of the supraoptic nucleus. The position of the cyst, and the marked denudation of cells in the remaining hypothalamic nuclei would adequately explain the postoperative disappearance of responses to ipsilateral intracarotid infusions. In the second animal, however, the hypothalamus was intact, although, as predicted, the whole of the anterior hypothalamic region on the side operated upon carried ipsilateral carotid blood, and had, therefore, been receiving an osmotic stimulus in the carotid infusion experiments. But a large cyst had appeared in the ipsilateral thalamus and had destroyed all the anterior and medial thalamic nuclei, having spread right up to the midline and caused degeneration of the thalamic paraventricular nucleus. Now in the hemispherectomized animal, in which, it will be remembered, responses to ipsilateral carotid

infusions had been retained, the heavy degenerative cell loss in the thalamus was coextensive with the cystic and degenerative destruction of thalamic nuclei in the animal now under consideration, with the exception that in the hemispherectomized animal the thalamic paraventricular nucleus and its connections with the hypothalamus had been preserved.

The evidence which is now present, therefore, leads to the conclusion that the osmoreceptors are in the anterior hypothalamic region, but that their functioning is dependent upon nervous connections with the thalamic paraventricular nucleus. This nucleus lies ventromedial to the stria medullaris—the stria is visible by the naked eye—and extends from the coronal level of the optic chiasma to that of the posterior commissure; and it will be of interest to know whether destruction of this nucleus is followed by a quantitative change in the osmotic responses to ipsilateral carotid infusions. The nucleus can be surgically exposed through the parietal cortex at anterior thalamic levels, and Howarth and I are now engaged in a specific enquiry on the status of this nucleus in the osmoreceptive process. It follows from what has been said that although the tiny vesicles which I described 10 years ago in the supraoptic nuclei lie within the osmoreceptive zone, there is no evidence as yet that they themselves mediate the osmotic release of antidiuretic hormone.

EFFECT OF ANTIDIURETIC HORMONE ON ELECTROLYTE EXCRETION

I come now to the question of whether or not the maintenance of near constancy in the osmotic pressure of the internal environment through the action of the antidiuretic hormone on water excretion is facilitated by an accompanying action on electrolyte excretion. I have already mentioned the fact that the inhibitory effect of postpituitary extract on the rate of water excretion by the perfused isolated kidney of the dog is associated with an increase in the rate of chloride loss. The dose of extract needed to produce these effects is, however, far greater—some 200 to 500 times—than that needed to produce comparable degrees of decrease in urine flow during water diuresis in the living dog; and here the evidence as to whether or not this decrease is associated with an increase in the rate of chloride excretion is conflicting. Andersson, Denton, and I decided, therefore, to investigate this question by determining, in an established water diuresis in the dog, the effects on the chloride and sodium excretion of superimposing for a limited time an infusion of postpituitary extract upon an infusion of sodium chloride at both the low and high rates.

The preparation of the animals for this investigation was similar to that previously described, but the method of urine collection was modified so that accurate serial measurements of the rate of electrolyte loss could be made. The catheter tube was cut short near the vulva and connected by T piece and rubber extension tubing with a glass delivery tube the nozzle of which was 20 centimeters below bladder level and emptied into a 10 milliliter burette with tap, placed immediately over the collecting flask. To the side arm of the T piece was attached a short piece of rubber tubing that was closed by a bulldog clamp. Before the collection of the first urine sample was begun, the bladder was drained, the clamp transferred to the extension tube, and 10 milliliters of warm sterile redistilled water were injected by syringe into the bladder. The clamp was transferred back to the side limb and the bladder redrained. This procedure was repeated twice, the complete return of the injected fluid being checked by means of the burette. As the last volume of distilled water was being injected a stop watch was started. Immediately after the bladder had been drained the clamp was transferred to the catheter, the extension tube drained and washed through with 5 milliliters of distilled water followed by air, and the clamp then replaced on the side

limb. Finally, the walls of the burette were washed down with 5 milliliters of distilled water, and a dry tared flask was placed below for the collection of the first urine sample.

The periods of collection were for about 10 minutes. The first was terminated by a repetition of this process, a second stop watch being started at the same time as the first was stopped. The periods thus followed continuously, and each was timed to the nearest second. The volumes of urine were determined by weighing each flask with its contents and subtracting therefrom the weight of the flask and the 40 milliliters of distilled water that had been used to wash the bladder, the collecting system, and the burette. The amount of chloride in each specimen was determined by Volhard's method, and that of sodium by flame photometry.

For the intravenous infusions, two syringes were used, and the plunger of each was propelled by a screw that was driven by a geared electric motor. Each syringe was filled with sterile liquid paraffin, and one was connected with the upper end of a glass bulb that contained the sodium chloride solution, the lower end being connected in turn with the infusing needle by means of polythene and a short length of rubber tubing. The second syringe was connected by a T piece with two bulbs one of which contained distilled water, the other postpituitary extract suitably diluted with distilled water; and each in turn was connected by polythene tubing with a needle inserted into the rubber tube to which the saline infusing needle was attached. Thus by clamping the connection between the syringe and one or other bulb, antidiuretic hormone could be infused or withheld without altering the rate of infusion of saline and water. With the smaller input of sodium chloride the solution entering the vein was a little hyptonic (137 millimolar), and with the larger input it was strongly hypertonic (1.37 and 1.23 molar). The rate of total fluid infusion, only 12.35 milliliters per hour, remained constant throughout the experiment.

Four primary types of experiment were made after the test dose of water had been given by stomach tube: first, control experiments in which the weaker solution of sodium chloride was infused; second, experiments in which postpituitary extract was infused for 30 minutes during the course of infusion of the weaker solution of sodium chloride; third, experiments in which the stronger solution of sodium chloride was infused; and fourth, experiments in which postpituitary extract was infused for a period of 30 minutes during the course of infusion of the stronger solution of sodium chloride.

In the control experiments there was no certain change in the rate of chloride excretion over the 140 minute period of slow infusion of the weak solution of sodium chloride. That is to say, with the gradual subsidence of water diuresis the concentration of chloride in the urine increased by some 5 times without significant change in the rate of chloride loss. Now if we assume that the total body water is 70 per cent of the animal's weight, that the original tonicity of this fluid is equivalent to that of a solution of sodium chloride containing 150 milliequivalents of chloride per liter, and that the osmotic effects of the water and chloride balances are evenly distributed therein, the course of the changing tonicity of the total body water during the experiment can readily be plotted. When this was done it was found—and this is, I think, of interest in view of the findings already alluded to in connection with the osmotic release of the antidiuretic hormone—that the urine flow began its consistently maintained fall when the osmotic pressure of the total body water had risen to 1 per cent below the isotonic level, and that the diuresis had subsided just when this level was reached.

In the second series of experiments postpituitary extract was infused for 30 minutes during the course of experiments otherwise

the same as those just described, and in none was there any certain change in the rate of chloride loss that could be related to the giving and the withholding of the extract and the large changes in urine flow that resulted from them. The doses of extract used were either 2 milli-units followed by the infusion of 1.2 micro-units per second or 5 milli-units followed by the infusion of 6 micro-units per second.

In the third series of experiments the stronger solution of sodium chloride was infused, and here the rate of chloride excretion increased apparently linearly during the infusion and while the diuresis was maintained. Between 60 and 70 minutes after the infusion was begun and between 100 and 110 minutes after the test dose of water had been given by stomach tube, the urine flow rapidly fell to some 10 per cent of its diuresis level, and with this fall the rate of chloride loss, after a temporary decrease, became accelerated. It was presumed that the inhibition of urine flow and its associated acceleration in the rate of chloride loss were caused by the endogenous release of antidiuretic hormone resulting from the increase in the osmotic pressure of the blood. Indeed it was found that when the course of the percentage change in the tonicity of the animal's total water phase was determined—on the assumption that the osmotic effects of the water and chloride balances were evenly distributed therein—the increasing osmotic pressure was passing through the isotonic level just at the period when the urine flow began its precipitous fall. It was of interest, therefore, to see whether both of these effects, viz., the precipitate fall in urine flow and its associated acceleration in the rate of chloride loss, could be antedated by the infusion of posterior pituitary extract before the expected time of their onset.

In all such experiments, infusion of the extract caused an acceleration in the rate of chloride excretion; and the subsequent recovery of urine flow was associated with an absolute fall in this rate. When, later, the final inhibition of urine flow supervened, presumably from endogenously released hormone, the rate of chloride loss increased once more. As in the previous series of experiments these last effects occurred just about the time when the rising tonicity of the animal as a whole was passing through the isotonic level. Thus the preceding antidiuresis and increased chloride loss from the infused extract were seen when the animal as a whole was definitely hypotonic. But at this stage the plasma sodium and chloride concentrations are, of course, higher than in those experiments in which infusion of the extract is without action on the rate of chloride loss; and I have found that if the fall in plasma sodium and chloride resulting from the absorption of the test dose of water is "corrected" by the intravenous injection of an appropriate dose of sodium chloride, then the antidiuresis from the infused extract is again accompanied by an increased rate of chloride loss. Thus, when this increase occurs, although the osmotic pressure of the extracellular fluid may be abnormally low, the concentrations of sodium and chloride ions are higher than they otherwise would be.

When, under the experimental conditions which I have outlined, the rate of chloride loss increases, as a result either of infusion of extract or of endogenous release of hormone, then the rate of sodium loss increases as well. The parallelism, however, is not a strict one; and there are many tempting experimental possibilities, both under the conditions of perfusion of isolated organs and under those surgically attainable in the living animal, of exposing and giving physiologic definition to the factors governing the release of the mineral corticoids and to the circumstances of their action on renal electrolyte excretion.

The perfusion conditions that obtain in the kidney in order that the antidiuretic hormone may cause an increased rate of chloride and sodium loss need experimental defining; but it is of interest, I think, that conditions may be imposed in the living

animal such that the chloride excretion response of its kidney to the hormone is similar to that of the isolated kidney perfused by a heart-lung preparation. Now in the early experiments with this preparation the serum sodium and chloride concentrations were abnormally high. In view of the information obtained from the living animal, it will therefore be of importance now to return to the heart-lung-kidney preparation in order to assess the relative significance of the plasma concentrations (at constant glomerular filtrate flow) of sodium and chloride ions on the one hand, and of the perfusion pressure (and so the filtrate load), on the other, as determinants of the antidiuretic hormone's role in augmenting the renal excretion of these electrolytes. Such investigations, consequently, are problems for the future.

Those of us who are attempting the objective analysis of some of the biologic phenomena of Nature and the subjective synthesis of the events that underlie them, "turning to shapes the forms of things unknown," will I think agree that, outside the ambit of family affection, there are few experiences more animating than the intellectual glimpse, howsoever imperfect and flickering it be, of biologic correspondences and functionally adapted processes. Much of the work that I have dealt with here has comprised observations on the living animal, and I have been encouraged to present them through the conviction that the degree of understanding of the phenomena of disease and the derivation therefrom of therapeutic control are closely dependent upon the degree to which relevant physiologic events can be experimentally exposed and accorded quantitative expression. For does not the work of the surgeon and physician breathe the tacit avowal that integration is the province of organism and environment, and disentitles data and events to simple transference beyond their conditioned field of origin?

The sanctions imposed by sensibility on the investigations of the doctor-surgeon and the physician thus become the discipline that governs the outlook and the work of the experimental physiologist. This is not to decry the partial subjection, in physiologic research, of the animal's living correspondence with its external and internal environments to the exigencies of experimental procedure and instrumental technique. Indeed, many of the data and much of the very vocabulary of physiology derive and, happily, will continue to derive from work of this kind. Rather is it a plea for more endeavor to resolve, through the matchless potentialities of surgery, the technical demands of these often conflicting perspectives, and so to bring recognition and measurement to events which, under other circumstances, may be masked or suppressed. If what I have said succeeds in some small measure in adding illustration to the interplay in biologic research between determination of properties and elucidation of function, and in inviting challenge to the assignment of quantity to events in a highly integrated milieu, I shall be much gratified.

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A TEN YEAR STUDY ON WOUND INFECTIONS

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THROUGHOUT THE CENTURIES one of the greatest obstacles to advancement in surgery has been infection. It has been only since the time of Lister that serious inroads have been made into the ravages of postoperative sepsis. In recent years the advent of the antimicrobial agents has further reduced the number of infections. However, despite all of these drugs, infection still occurs. Because of this fact it seemed advisable to review the recent experience at this center to see if there are trends in infection rate developing with the use of the newer drugs, and whether more stringent precautions should be introduced.

MATERIALS AND METHODS

The hospital records were reviewed of all pavilion patients with wound infections occurring between January 1, 1947 and December 31, 1956, on the general surgical service and surgical specialties. There was a total of 511 wound infections during this period. These form the basis of this study.

Wound cultures were inoculated for primary isolation both aerobically on blood agar plates and in 3 per cent beef infusion broth, and anaerobically in liver dextrose broth. Recently, since the establishment of the surgical bacteriology laboratory, staphylococci have been characterized by mannitol fermentation, coagulase production, antimicrobial susceptibility profile and phagetyping as well as by the production of hemolysin and pigment.

Drug sensitivity tests were not done except by the disc method, and in the earlier years of this study these were carried out only upon request. The procedure presently employed is the serial tube dilution as described by Rammelkamp.

Analyses were made of yearly and monthly incidence, surgical service involved, and species of organisms involved.

RESULTS

The total number of operations performed each year on the pavilion (ward) surgical services has remained reasonably constant during the period of study, ranging from 4,900 to 5,700, with the exception of 1947 during which only 3,400 operations were performed (Fig. 1). As presented in Figure 2 one may consider the fluctuations in incidence of wound infection best in terms of the actual number each year, since the rate has varied from 0.8 to only 1.4 per cent each year with an over-all rate of 1.0 per cent. The proportion of infections due to enteric organisms has not varied significantly. In contrast the number of infections due to staphylococci has fluctuated considerably. The years 1949, 1952, and 1953 represent peak years in staphylococcal infections. It is suggested that greater use of tetracycline compounds at that time may have been a factor, as discussed later.

Although the number of infections due to the miscellaneous group of organisms varied little from month to month, a peak incidence of staphylococcal infections was in March and December of each year (Fig. 3).

The anatomic location of infected wounds was roughly proportional to the over-all frequency of operations involving an area. Wounds created for operations upon the bowel or urinary tract were infected more commonly with the enteric organisms. In contrast the wounds of operations not involving the urinary tract or intestine were caused by staphylococci in the great majority of cases. This fact is well illustrated by

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TABLE I.—WOUND INFECTIONS, PAVILION SURGICAL SERVICES, THE NEW YORK HOSPITAL—CORNELL MEDICAL CENTER, 1947 TO 1956

Year	Surgical I	Surgical II	Surgical III	Neuro-surgery	Plastic surgery	Fracture orthopedic	Urology	ENT	Eye	Total
1947	14(9)*	11(5)	7(4)	10(7)	5(4)	0	0	0	0	47(29)
1948	11(4)	9(3)	10(3)	8(8)	0	0	1(0)	0	0	39(18)
1949	15(5)	15(8)	11(6)	9(7)	6(5)	0	4(2)	0	0	60(33)
1950	14(3)	8(2)	11(4)	4(4)	5(3)	1(1)	2(1)	0	0	45(18)
1951	13(4)	12(7)	11(4)	2(2)	3(3)	0	5(1)	0	0	46(21)
1952	17(11)	22(19)	21(14)	3(2)	6(5)	1(1)	3(1)	0	0	73(53)
1953	11(5)	25(15)	15(8)	3(3)	7(6)	1(1)	2(1)	0	0	64(39)
1954	5(3)	9(4)	11(5)	3(3)	5(5)	2(2)	3(1)	0	0	38(23)
1955	9(6)	12(8)	15(10)	3(3)	6(6)	1(0)	3(1)	0	0	49(34)
1956	7(3)	10(3)	17(9)	5(4)	4(3)	3(2)	2(0)	0	2(2)	50(26)
Total	116(53)	133(74)	129(67)	50(43)	47(40)	9(7)	25(8)	0	2(2)	511(294)

*Figures in parentheses represent number of staphylococcal infections.

TABLE II.—PERCENTAGE INCIDENCE OF WOUND INFECTION, PAVILION SURGICAL SERVICES, THE NEW YORK HOSPITAL—CORNELL MEDICAL CENTER, 1947 TO 1956

Year	Service total	Surgical I	Surgical II	Surgical III	Neuro-surgery	Plastic surgery	Fracture orthopedic	Urology	ENT	Eye
1947	0.9(0.6)*	1.6	1.2	0.8	2.9	2.0	0	0	0	0
1948	0.8(0.4)	1.0	0.9	1.0	2.1	0	0	0.2	0	0
1949	1.1(0.6)	1.4	1.7	1.1	2.1	2.1	0	0.7	0	0
1950	0.8(0.3)	1.3	0.8	1.1	1.0	1.7	0.7	0.3	0	0
1951	0.9(0.4)	1.4	1.3	1.5	0.6	0.9	0	0.9	0	0
1952	1.4(1.0)	2.3	2.5	2.2	0.9	1.7	0.6	0.5	0	0
1953	1.4(0.8)	1.6	2.6	1.6	0.8	2.0	0.9	0.4	0	0
1954	0.8(0.5)	0.7	0.8	1.1	0.7	1.4	1.8	0.6	0	0
1955	1.0(0.7)	1.3	1.2	1.5	0.9	1.7	0.5	0.5	0	0
1956	0.9(0.5)	0.9	0.9	1.7	1.6	1.1	1.1	0.4	0	0.6

*Figures in parentheses indicate percentage incidence of staphylococcal infections.

TABLE III.—OPERATIONS AND WOUND INFECTIONS, PAVILION SURGICAL SERVICES, THE NEW YORK HOPSITAL—CORNELL MEDICAL CENTER, 1947 TO 1956

Service	Surgical I	Surgical II	Surgical III	Neuro-surgery	Plastic surgery	Fracture orthopedic	Urology	ENT	Eye	Total
Operations	8586	9698	9543	3620	3244	1419	5711	6243	3431	52,022
Wound infections	116(53)*	133(74)	129(67)	50(43)	47(40)	9(7)	25(8)	0	2(2)	511(294)
Rate in per cent	1.2(0.6)	1.3(0.8)	1.3(0.7)	1.4(1.2)	1.4(1.2)	0.6(0.5)	0.4(0.1)	0	0.1(0.1)	1.0(0.6)

*Figures in parentheses indicate number and percentage incidence of staphylococcal infections of total operations.

the data obtained from the neurosurgical, plastic, and fracture and orthopedic services. In each of these over 85 per cent of infections were due to staphylococci.

Only 29 of the 511 infections were due to beta hemolytic streptococci, and among these there was no yearly or seasonal incidence of note.

Table I shows the annual incidence of wound infections on each general surgical service and on the surgical subspecialties. Table II records the percentage of total operations in which wound infections occurred. Table III is a summation of the over-all 10 year experience on these services. It is of interest that the incidence is quite similar except for the percentage of the total infections caused by staphylococci on the neurosurgical, plastic, and fracture-orthopedic service.

DISCUSSION

Infections that occur in the postoperative state are in the great majority of instances caused either by the staphylococci or by one or more of the enteric flora. From inspection of Figures 2 and 3 it is evident that the incidence of wounds infected with bowel flora has not appreciably changed in the past 10 years and the seasonal curve does not indicate any significant variation. Because more wounds are infected with staphylococci and in view of the current intense interest in this problem the present

survey was made. In addition, subsequent fluctuations in infection rate may be seen in better perspective, weaknesses in technique may be detected more easily, and the attention of the professional staff may be directed to the problems involved.

It is extremely difficult to evaluate the "staphylococcal problem" in one institution or in the nation as a whole. However, McDermott has recently presented the views of many observers in this field. He states: ". . . the 3 principal diseases involving bacteria that are most prominent in the United States are those diseases produced by the bowel flora, by tubercle bacilli, and by staphylococci. These three groups of diseases have a number of features in common. Above all, they share in the fact that harboring of the parasite is commonplace but disease is rare. This means that the spread of these diseases among a group of persons is not to be regarded as a visitation from without but rather as an indication that something is going wrong with the crude equilibrium that had previously existed in that community. Our preoccupation should be with attempts to discover what it is that goes wrong that permits these 'hangers-on' to gain control. Or, more specifically, we should be concerned with a study of what there is to go wrong." In speaking further about staphylococcal infections and studies on this subject he goes on to say: "We have sinned further, in my opinion, by not clearly pointing out that most of the large-scale clinical investigations on drug-resistant staphylococci were not concerned with staphylococcal disease at all, but had to do with something quite different: namely, the healthy carriers of staphylococci . . . until recently we quite failed to emphasize something we all knew, namely, that a penicillin-susceptible staphylococcal infection in a patient virtually never becomes penicillin-resistant during therapy." The problem basically is that many patients in the hospital today are those who have chronic illnesses which are arrested by more modern adjuncts of therapy. Yet they do not have the defense mechanisms necessary to combat infection.

FIG. 1. Number of operations performed in the Department of Surgery, The New York Hospital—Cornell Medical Center from 1947 through 1956.

In 1920 Douglas, Fleming, and Colebrook reported on their studies of wound infections carried out during World War I. This interesting and careful work contained a review of 61 wounds. All but 9 were primarily or secondarily infected with staphylococci. However, the authors stated: "Staphylococci . . . are commonly found in wounds but as they are the same as those which flourish in the ordinary open wound no detailed description of their character is necessary." The staphylococci were considered as mere contaminants of little importance. By 1938 there was a decided change in this belief. Ives and Hirshfeld reported a 5 per cent incidence of infection of clean surgical wounds. Of these, from 50 to 70 per cent were caused by staphylococci. Thus, this organism was appreciated as a true postoperative hazard.

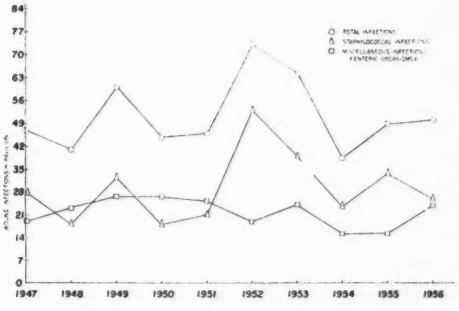

FIG. 2. Ten year incidence of wound infections in ward patients from 1947 through 1956.

The factors involved in wound infections can be grouped conveniently under three headings: (1) breaks in aseptic technique, (2) host-parasite relationship, and (3) persistent organisms.

Breaks in technique. This is an all inclusive term and refers to the methods by which pathogenic bacteria are delivered to the wound. Theoretically each surgical department has evolved a set of precautions which, when followed exactly, prevents bacterial contamination of wounds. There are obviously many ways in which contamination could occur. Some of the commoner methods are illustrated by the following examples.

Sompolinsky and associates reported in 1957 an outbreak of pure staphylococcal wound sepsis in a thoracic surgical unit in Israel. At one point, 37 per cent of all wounds became infected. By a careful epidemiologic study 2 operating room nurses were incriminated. These 2 people were staphylococcal carriers, but, more important, it was noted that on occasions when in the operating room but not scrubbed, they would lower their masks to converse. These and similar practices were stopped and the wound infection epidemic ceased, although the nurses remained carriers.

Blowers and associates also reported their experience with an extremely serious outbreak of staphylococcal wound infections in a thoracic surgery unit, which required temporary closure of the unit. The careful bacteriologic studies carried out revealed a high incidence of nasal carriers of staphylococci among the personnel. However, perhaps even more important were the high Staphylococcus aureus counts obtained from air sampling of the wards and operating rooms. This was attributed in part to faulty ventilation and to lack of isolation facilities. It is of interest that even the blankets were heavily contaminated, and this was true as well when they were freshly laundered. These staphylococci were almost all penicillin-resistant. It was the conclusion of the authors that these organisms entered the wound at the time of operation by the air-borne route. This entry occurred either in bringing contaminated blankets into the operating rooms and shaking them out, or by personnel not changing infected clothing. The authors believe the staphylococci reach the wound by the air-borne route but are brought to the operating room by a contaminated vector.

Shooter and associates found in a series of wound infections studied recently that the Staphylococcus aureus responsible in each case usually fell into a different phage group which observation is in contradistinction to most published reports. They also noted that the principal surgeons were not nose or hand carriers. The surgical wards, however, did have high staphylococcal air counts, and the ventilating system was found to bring the ward air directly into the operating room. When this fault was corrected the incidence of wound sepsis dropped precipitously. The authors attribute these infections to air-borne bacteria, and a break in the asepsis of the operating room ventilation.

Host-parasite relationship. This relationship is a broad title to encompass a group of factors important in the genesis of wound infection. Much has been written about the carrier state of staphylococci. Miles in 1944 reported that about 50 per cent of 1,000 normal adults entering the hospital for the first time were carriers of staphylococci. About 10 per cent of these 1,000 patients were consistently positive by follow-up studies in the hospital, while about 10 per cent of them never carried staphylococci.

Howe noted at the Massachusetts Memorial Hospital a stepwise increase of wound infections over a 5 year period. Positive cultures of staphylococci were obtained from the hands or noses of 99.2 per cent of the personnel and patients. Of these staphylococci 78.5 per cent were penicillin-resistant. Howe attributed the rise in wound infection rates to the tremendously increased exposure of wounds to staphylococci. He recommended an increased vigilance by all personnel in protecting themselves from be-

coming carriers and extreme care in the operating room to prevent passage of organisms from nose to wound.

The fact that so many of these organisms are penicillin-resistant has caused a great deal of concern. Clarke has demonstrated that staphylococci colonize a nose more readily if no other staphylococcus is present. Thus when antimicrobial drugs are given systemically, the susceptible organisms are removed from the nose, and the area is open for colonization by resistant microbes.

Another, and probably extremely significant fact in wound sepsis, is the "resistance of the host." Rantz has presented convincing evidence that an anatomic or physiologic deficit in the host, for example diabetes, hypothyroidism, or cachexia, permits infection to become a clinical disease entity more readily. One of us (4) has recently reported such an instance. It is a well known fact that diabetics are more subject to infection, and this fact is attributable apparently to a host deficit, i.e., an inability to combat the infection or to establish a satisfactory equilibrium with it.

Drug resistance of staphylococci as a cause of wound infection is difficult to evaluate. The majority of infections arising in the hospital are caused by organisms resistant to penicillin and often to other antimicrobials as well. It might, therefore, be supposed that these bacteria are more virulent than their susceptible brothers. As Barber has shown, penicillin resistance apparently does not occur clinically in an infection under penicillin treatment. If penicillin resistance does appear there is a change in phage type which very strongly suggests that a different strain has taken over. However, resistance to streptomycin and to the tetracyclines does take place in vivo, in a stepwise fashion. These characteristics of the parasite apparently do not make the organisms more pathogenic. Over a course of time, however, as Howe has shown, an environment may become completely saturated with this type of "hospital" organism. Therefore, if contamination takes place, it almost certainly would have to be with the resistant strains.

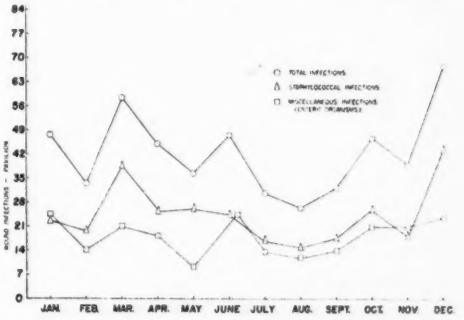

FIG. 3. Monthly incidence of wound infections during 10 year period from 1947 through 1956.

Persistent organisms. The presence of persistent organisms represents a phenomenon in which viable organisms can remain in living tissue for long periods without causing clinical disease and without becoming drug-resistant. These organisms under certain circumstances of stress can be evoked and cause disease. Experimentally, this has been demonstrated with the Staphylococcus aureus. Clinically it is seen in such conditions as the exacerbation of a "dormant" osteomyelitis following remote trauma. What part this phenomenon plays in wound sepsis is not clear, but certainly it is a clinical observation that apparently clean wounds have been known to break down months or years after surgery. Also sites of abscess drainage, particularly in the breast, may show a recrudescence of infection after a long quiescent period. Thus an operation through a scarred area may not be as aseptic as once supposed.

From the observations made of the past 10 year period at this center it is impressive that the peak months of wound infections (December and March) coincide with the peak months of upper respiratory tract infections. These semiannual rises have occurred in the same months in every year. Nasal cultures of 5 surgeons doing most of the major pavilion surgery showed them to

have coagulase-positive penicillin-resistant Staphylococcus aureus present during March and April of 1957. In March there were 10 staphylococcal wound infections and in April none. Therefore, it is apparent that the mere carrying of staphylococci does not cause wound infection. A combination of factors must be present. Of these one of the most important seems to be the nasopharyngeal flora of the surgical team. A policy has been instituted at this Center of wearing masks while doing open dressings in the pavilions. It is not only important to have these regulations but to enlist the co-operation of all who have contact with the patients, particularly in the operating room.

It is not practical in many institutions, including this one, to attempt to establish a so-called "isolation ward." Even if this were done, it does not seem to be the logical answer, for the staphylococci are so widespread in our society as a whole that no practical means of totally excluding these organisms are available. Since it is generally accepted that wound sepsis is initiated in the operating room in most cases, it seems best to concentrate our efforts at this point.

Infections caused by enteric organisms. Infections caused by enteric organisms have remained at a fairly constant level during the 10 years of this study. Most infections in this group are caused by one or more of the following: Escherichia coli, Aerobacter aerogenes, Pseudomonas pyocyaneus, Proteus vulgaris, Klebsiella pneumoniae, Bacteroides fusiformis, Clostridium welchii and enterococci. These have all been associated to some degree with devitalized or necrotic tissue, poor local blood supply, foreign body, or large inadequately drained "dead spaces."

Some of these are directly attributable to breaks in technique. Others, and the majority, represent contamination of devitalized or poorly nourished areas by fecal material, as for example, amputation stumps in elderly patients with arteriosclerosis and anal incontinence, colostomy closures, or operations on gangrenous bowel.

There seems to be a certain number of this type of infection that will occur every year despite all efforts. Yet, it is hoped that by greater caution these too may be reduced.

SUMMARY

A 10 year study of wound infections at The New York Hospital—Cornell Medical Center reveals an over-all incidence of 1 per cent. Fluctuations in the annual number of infections are comprised almost exclusively of staphylococcal infections.

Peak months for staphylococcal wounds in this center are March and December.

Wound infections are usually caused by breaks in technique, a weakened host resistance, or by "persistent" organisms.

Increased vigilance on the part of the professional staff is probably the single most important factor in prophylaxis. Attention should also be directed to adequate face masks, operating room ventilation, and to the prevention of the "carrier state" by the patient and professional staff.

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EXPERIENCE WITH TRIETHYLENE MELAMINE (TEM) AND TRIETHYLENE THIOPHOSPHORAMIDE (ThioTEPA) IN RECURRENT OR METASTATIC SOLID TUMORS

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THE TIME COMES all too frequently in the day-to-day practice of every surgeon when the high hopes and enthusiasm with which he has instituted treatment for cancer are shattered as the patient returns with inoperable metastases. Our purpose is to report our experience with triethylene melamine (TEM) and triethylene thiophosphoramide (Thio-TEPA, TSPA) in 40 patients with advanced, "hopeless" cases of carcinoma in whom all curative and all established palliative measures had failed or were contraindicated, and to offer another tool for palliation in such instances.

It must be emphasized that a study such as this does not lend itself to statistical analysis, and the results reported, good and bad, can only be interpreted in the light of knowledge of the natural history of the tumor under consideration.

MATERIALS AND METHODS

The cases presented herein have been gathered from private and clinic sources in and near San Francisco, and have all been seen and followed up by one or both of the authors. Varied lesions and modes of treatment existed to such a degree as to make tabulation difficult. Consequently the cases were grouped by anatomic location and pathologic diagnoses to facilitate presentation. Many reports are to be found in the recent literature concerning the use of the antitumor compounds, TEM and Thio-TEPA, but many are related to their use in "nonsurgical" neoplasia. Other tumor chemotherapeutic drugs, such as leukeran, actinomycin D, and phenylalanine mustard have occasionally proved useful, but our experience with them is as yet limited and will be the subject of future reports.

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TREATMENT

The purpose of instituting treatment in these advanced cases was twofold: (1) to determine whether or not these agents significantly inhibited tumor growth, and (2) to attempt to make the patient's final remaining days as comfortable as possible. In some cases the result was startlingly successful; in some, an apparent failure. However, the treatments per se did not ordinarily impose a severe burden on the patient's financial or physiologic economy, and in many cases gave a great psychologic "lift" by offering some relief to an intolerable situation. An attempt was made to report as benefited only those patients showing objective tumor regression in order to avoid, insofar as possible, the effects of psychic benefit.

ThioTEPA. This drug was given as an injection of a solution containing 10 to 20 milligrams per cubic centimeter by any of three routes: (a) intramuscularly for general effect; (b) into serous cavities to attempt to control malignant effusions; and (c) directly into tumor masses. The latter method was particularly advantageous when local masses were producing the major symptoms by pressure, erosion, or infiltration of vital structures, and had the added advantage of allowing larger doses to be given without producing as pronounced a

depression in hematopoiesis as was encountered with the other routes. In adults, when the intramuscular route was utilized, 20 to 30 milligrams per week were given in 1 to 3 divided doses. Blood counts were performed before each injection, and if leucopenia or thrombocytopenia occurred, the dose was reduced or treatment discontinued. When injected into serous cavities, the individual doses varied from 20 to 40 milligrams, and the drug was instilled after the fluid had been removed. The dose often was diluted in 100 cubic centimeters of normal saline solution and the patient was encouraged to change position frequently after the injection to insure even distribution. It appeared that all of the drug was rather rapidly absorbed after this route of injection, and, therefore, the use of this modality was limited as to frequency. Direct injection of THIOTEPA into a tumor mass proved very useful in several cases. Individual injections ranged from 40 milligrams to as high as 100 milligrams and appeared to produce less toxic effect on the hematopoietic system than did the other routes. Before each injection, the drug was diluted to a convenient volume with normal saline solution or with a local anesthetic solution. General anesthesia was usually unnecessary, although analgesics were frequently used. The overlying tissues were infiltrated with a local anesthetic and the drug was injected directly into the tumor either at a single site, utilizing a fanning technique, or by means of multiple punctures. Hyaluronidase also was used as a spreading agent, and in some instances epinephrine was employed to produce vasoconstriction and delay systemic absorption of the drug.

TEM. This compound may also be utilized in a variety of ways, and has the advantage of being effective when given by mouth. In this series it was utilized most frequently by being instilled into a serous cavity in the manner before stated in a dosage of 5 to 10 milligrams. Subsequent therapy consisted of the oral administration of the drug in divided doses of 2 to 5 milligrams a week, given with bicarbonate of soda ½ to 1 hour before breakfast to lessen gastric irritation and to promote absorption. Occasionally TEM was given by intramuscular injection or by direct injection into tumor masses, but it seemed to have limited usefulness in this respect because of the convenience of oral administration and because of its profound cytotoxic effect leading to massive necrosis when injected into tumor tissue.

It should be pointed out that failure to respond to one agent does not preclude the possibility of response to another drug, and many of these patients have had metachronous courses of therapy using several agents.

COMPLICATIONS AND CONTRAINDICATIONS

As with all potent drugs, the physician should acquaint himself with the pharmacology and toxicology of these compounds prior to undertaking treatment. Good reviews by Hall, Humphrey, Sykes (5), and their associates are available, and the literature is replete with studies of the effects of other alkylating agents whose properties are similar to the drugs under consideration. The manifestations and complications of leucopenia and thrombocytopenia are the most frequent undesirable side effects and must be watched for carefully. It is imperative that the dosage schedule for these drugs be individualized, as the effect on the bone marrow varies greatly from one patient to the next; the same dosage may completely suppress hematopoiesis in one individual, while giving only mild leucopenia in another. In practice, it has been possible to carry patients for prolonged periods with total white blood cell counts of around 2,000 cells per cubic millimeter without serious consequences, provided the patients are alerted to report even trivial signs of infections. Manifestations of hemorrhage were infrequent in this series even with platelet counts below 50,000 cells per cubic millimeter. While it is redundant to say that suppression of hematopoiesis is undesirable, occasionally good control of a tumor can be

gained only by employing dosages which are large enough to produce these side effects. Anemia sometimes becomes severe enough to require transfusions, but it is often difficult to know whether this problem is due solely to therapy or to the effects of the widespread malignancy. Prednisone in rather large doses (20 to 40 mgm. daily) has been tried empirically to decrease the tendency toward anemia with equivocal results. More studies are needed about the effects of steroids on the anemia of cancer before the value of this therapy can be fully assessed.

When chemotherapy is used in conjunction with radiation therapy, hematopoiesis is placed in double jeopardy; consequently, although apparent synergism of these modalities has been observed, combined therapy should be approached with unusual care. It would indeed be unwise to be forced to discontinue radiation therapy short of optimum doses because of the injudicious use of the drug.

The other complications we have seen have been related to local cytotoxic effects, such as occasional weeping erythema of the skin overlying injected tumor masses and general symptoms of toxicity with fever, from breakdown of large intra-abdominal tumor masses, and in 1 case, an intestinal perforation which could have been caused by necrosis of tumor tissue that was an integral part of the intestinal wall (*vide infra*).

A practical contraindication is the complete lack of beneficial effect in certain types of malignant neoplasms, as will be noted later.

CASES AND RESULTS (TABLE 1)

Head and neck. Three patients with squamous cell carcinoma and 1 with lymphoepithelioma locally recurrent or metastatic to regional nodes or to the lung were treated by local or systemic therapy with THIOTEPA, intrapleural instillation of TEM, or both. As has been the experience with epidermoid cancers elsewhere in the body, no beneficial effects were obtained.

TABLE I.—RESULTS

Region and type	*No. of cases*	*No. improved*	*No. unchanged*
Head and neck			
Squamous cell	3	0	3
Adenocarcinoma	2	1	1
Breast	5	4	1
Chest and esophagus	2	0	2
Gastrointestinal tract	7	4	3
Female internal genitalia			
Ovary	11	10	1
Uterus	3	3	0
Skin and extremities	4	0	4
Other	3	1	2
Total	40	23	17

In 1 case of recurrent carcinoma of the parotid involving orbit, base of skull, maxilla, and hard palate treatment was by 2 injections of THIOTEPA of 80 and 100 milligrams respectively. Moderate diminution in size of the mass was observed and marked relief of pain occurred which continued until the patient's death elsewhere 2 months later of apparent airway obstruction.

One patient with anaplastic adenocarcinoma of the thyroid with mediastinal and pulmonary involvement was temporarily subjectively benefited by the systemic use of THIOTEPA given in a dosage of 10 milligrams every other day to a total dose of 80 milligrams with some improvement in breathing, but no objective evidence of tumor regression.

Breast. Five patients with carcinoma of the breast were treated, and some of the most prolonged good results occurred in this group. Paradoxically, the intrapleural use of either THIOTEPA or TEM was uniformly unsuccessful in controlling pleural effusions caused by metastases of breast cancer. Good response to the local injection of recurrent masses with THIOTEPA was observed. Preinjection and postinjection biopsies of superficial nodules revealed a marked decrease in tumor cells and an increase in fibrous tissue, but no histologic evidence of alteration in the remaining tumor cells. The explanation for this finding is not apparent.

The following is an illustrative case:

A 75 year old white female was first seen in February of 1956, with an ulcerated, weeping carcinoma

en cuirasse involving most of the right anterior chest, axilla, medial upper arm, and right scapular region. Local discomfort was marked and there was hyperesthesia of the skin of the right arm, presumably due to brachial plexus involvement; the drainage was odorous and difficult to control. The patient had had a radical mastectomy 12 years previously, followed by postoperative roentgen therapy and a second course of irradiation carried to skin tolerance, with the onset of the recurrence 11 years later. She had also received androgens with temporary benefit. Local treatment consisted of aluminum subacetate moist compresses, and the patient was given THIOTEPA in doses of 20 milligrams per week intramuscularly. The pain and hyperesthesia cleared, lesions epithelialized within 2 weeks, and she required no more than occasional salicylates for 8 months until thrombocytopenia forced reduction in dosage and finally discontinuance of the drug. At that point the patient was given a trial of estrogen therapy with almost immediate subjective and objective evidence of increased tumor growth. THIOTEPA was once again utilized with remarkable control of the tumor, even on a lowered dosage schedule, suggesting a "re-sensitization" of the tumor coinciding with the increased growth rate. The hematopoietic depression necessitated 3 transfusions and presently allows only occasional injections of the drug; but at this time (17 months after institution of therapy) the patient is able to carry out limited social and household duties with minimal discomfort and she recently presided over a celebration of her fifty-third wedding anniversary. The patient has had over 500 milligrams of THIOTEPA during the 17 months' period.

Chest and esophagus. In 1 case of squamous cell carcinoma of the lung and 1 of the esophagus treatment has been with systemic THIOTEPA without evidence of palliation.

Gastrointestinal tract. Seven cases of adenocarcinoma of the stomach and intestines have been treated. Two were primary in the stomach, 1 in the jejunum, 3 in the colon and rectum, and 1 abdominal carcinomatosis with the primary site undetermined. In 3 of these cases ascites or pleural effusion was the predominant symptom and was handled by the intraperitoneal instillation of TEM followed by an oral dosage schedule. In each of these cases there was satisfactory control of fluid formation obviating the need for repeated paracenteses. In 2 cases this effect continued until death 5 months later. However, no objective change was noted in the gradual progression of the tumor masses. In 1 case no paracenteses were required for 3 months. Then gradual reaccumulation of fluid occurred, requiring evacuation at longer intervals than before therapy. In this last case reduction in size of the gastric neoplasm by about one-half was noted by x-ray examination, and a pleural effusion which developed early in the course of therapy resorbed without thoracentesis.

Three patients were treated by systemic or intratumor injections of THIOTEPA without alteration in objective findings, although 1 patient with partially obstructing adenocarcinoma of the sigmoid experienced temporary relief of diarrhea and cramping pain. Fluid formation was not a problem in these cases.

The palliation obtained in a case of adenocarcinoma of the jejunum was of an unusual nature insofar as the primary problem was recurrence in an upper midline surgical scar, with severe pain apparently secondary to involvement of the periosteum and perichondrium of the costal arch. Three local injections of THIOTEPA of 30 to 40 milligrams each produced, in the patient's words, "90 per cent relief of pain" and palpable softening and regression of the tumor. At the time of this writing, this effect had continued for 4 months after the last injection. Following the injections, a weeping superficial ulceration suggestive of a radiation dermatitis developed, but cleared spontaneously with symptomatic local therapy.

The only other complication noted in this group of patients was a single instance of pancytopenia and ulcerative stomatitis which responded promptly to antibiotics, 1,000 cubic centimeters of whole blood, and temporarily stopping administration of the drug.

Female internal genitalia. We have observed 8 cases of serous cystadenocarcinoma of the ovary, 2 cases of pseudomucinous cystadenocarcinoma of the ovary, and 3 of adenocarcinoma of the endometrium.

As reported by Bateman and Sykes (6) and their associates, the response of ovarian

tumors to these agents often is most gratifying, particularly in the serous cystadenocarcinomas. Depending on the clinical problem involved, the mechanism of treatment has been either instillation of TEM into the peritoneal or pleural cavities followed by oral administration of the drug, or the direct injection of THIOTEPA into tumor masses. By transrectal or transvaginal injection into tumor masses, 2 palliative colostomies have been averted with satisfactory control of tumor growth until death intervened from some cause other than low intestinal obstruction.

The 1 patient who failed to respond had a serous cystadenocarcinoma with ascites that had likewise been unresponsive to heavy irradiation and to the instillation of radioactive chromic phosphate.

The response of the endometrial adenocarcinomas to treatment has not been as dramatic as that observed with the ovarian tumors, but, nevertheless, has been definite in each case. In one, marked diminution in vaginal hemorrhage occurred; in another, massive lymphedema of the legs subsided; and in the third, relief of a partial bowel obstruction was obtained. The effects were more transient, however, than was noted in the ovarian tumors.

Two major complications occurred in this group of cases and will be discussed in detail. In a case of pseudomucinous cystadenocarcinoma of the ovary, the patient returned 3 weeks after intraperitoneal drug administration with a large, tender mass in the region of the paracentesis which, on surgical evacuation, proved to contain intestinal contents. Although it is possible that this was due to spontaneous rupture of the intestine at a point weakened by tumor infiltration, or an accidental perforation of a loop of intestine by needle trauma, the possibility of necrosis of tumor-infiltrated bowel wall secondary to the action of the drug also must be considered. This possibility is enhanced by the gelatinous nature of the fluid in this type of tumor which would inhibit diffusion of the drug.

The second complication occurred in a patient with a serous cystadenocarcinoma who had a 12.5 centimeter solid mass in the right lower quadrant, ascites, pleural effusion, mediastinal nodes demonstrable by x-ray, and proved metastasis in a left supraclavicular node. The patient was admitted to the hospital because of symptoms secondary to the ascites and almost complete small bowel obstruction. Because of the widespread nature of the disease and the severity of the symptoms, vigorous therapy was instituted with the injection of 10 milligrams of TEM and 150 units of hyaluronidase into the mass in the pelvis and the concomitant use of systemic THIOTEPA. Although the fluid accumulation was controlled and the obstructive symptoms abated, the patient became febrile and toxic and gradually declined to her death 6 weeks later. Investigations to determine the source of fever were unproductive and the patient had only a transient, mild leucopenia. At autopsy, no viable tumor could be found, with the exception of a small lymph node in the mediastinum which was replaced by tumor, and the previously solid mass in the pelvis was now a fibrous shell filled with hemorrhagic necrotic material. It was to be surmised that the treatment had been somewhat too vigorous and the already overburdened economy of the patient had been unable to withstand the additional necessity of resorbing so much necrotic tissue.

Skin and extremities. Three patients with malignant melanoma have shown no evidence of response to systemic THIOTEPA; although in 1 case, transient improvement was obtained by direct injection of THIOTEPA into several painful nodules. The natural history of this tumor makes this effect impossible to evaluate. One case of Ewing's sarcoma with pulmonary metastases likewise showed no improvement to systemic THIOTEPA.

Miscellaneous. An inoperable lymphosarcoma arising in the radix mesenterii was treated concomitantly by irradiation and systemic THIOTEPA, with satisfactory control of the local tumor. The location of the

original tumor was treated to the full dose planned by the radiologist, but the appearance of a leucopenia precluded irradiating the surrounding areas as a prophylactic measure. No evidence of local recurrence is present after 20 months, but a proved metastasis to a left preauricular node and suspected metastases to several superficial cervical nodes have manifested themselves. The metastases have shown no evidence of enlargement in 1 year.

One inoperable clear-cell carcinoma of the kidney was treated by 1 intratumor injection of a rather small dose of THIOTEPA in our study with no demonstrable effect.

One child with a retroperitoneal tumor reported to be an embryonal carcinoma, which recurred almost immediately after irradiation, was given multiple chemotherapeutic agents. There was no evident response to systemic THIOTEPA in this patient.

The experience with local injection of THIOTEPA into transitional cell carcinomas of the bladder has been encouraging and will be reported by Schulte.

DISCUSSION

As with all palliative therapy, the results obtained in this series fall far short of the desired level; but in the individual patient by whom a satisfactory response has been obtained, even for a limited period of time, they are most gratifying. Every doctor who has been faced with the necessity of telling a patient or his family that "everything has been done," or the occasional even more odious task of performing a palliative operation, will realize that the use of chemotherapeutic agents in selected cases can prove to be a welcome adjunct in the handling of malignant tumors.

In searching for other ways to utilize the knowledge gained from the treatment of advanced cases of carcinoma, it has occurred to several workers in this field that the use of prophylactic administration of carcinocidal agents at the time of surgery to render the soil less fertile for the implantation of cancer cells could well be helpful. This procedure we have started on a limited scale with the use of a single intramuscular or intravenous dose of THIOTEPA immediately following surgery for carcinoma of the breast, and the intraperitoneal administration of TEM following extirpative surgery for abdominal cancers; and it is hoped to expand this study in the future. Needless to say, much time will elapse before an adequate evaluation of this type of work can be obtained, as it must await statistical consideration. It may well be that the tremendous advances which are being made in our understanding of the biochemical fundamentals of this disorder will outstrip the plodding but imperative approach of the clinician. However, we should make use of all available equipment to improve our presently rather dismal record while awaiting a more logical solution to the problem.

SUMMARY

Our experience with a series of 40 patients with advanced malignant disease who have been treated with the chemotherapeutic agents, triethylene melamine and triethylene thiophosphoramide, and in whom adequate clinical and follow-up data were available, forms the basis of this report. General conclusions which may be drawn from this study are:

1. A clinical response was obtained in several cases of adenocarcinoma, particularly those primary in the breast, by systemic therapy with THIOTEPA or the injection of this agent directly into tumor masses.

2. TEM appears from this study to be preferable to THIOTEPA in the control of malignant effusions.

3. No effect from either of these agents was seen in squamous cell tumors or in mesenchymal tumors arising in organs other than the lymphatic system.

4. The depressant effect of these agents on the bone marrow was the chief cause of complications. Other complications have been less frequent and have been discussed in detail.

5. In selected cases the use of the antitumor compounds, TEM and THIOTEPA, has been of assistance in easing the distress of terminal cancer cases.

A possible mechanism of using these or other tumor chemotherapeutic agents as a means of prophylaxis against surgically spread metastases is suggested.

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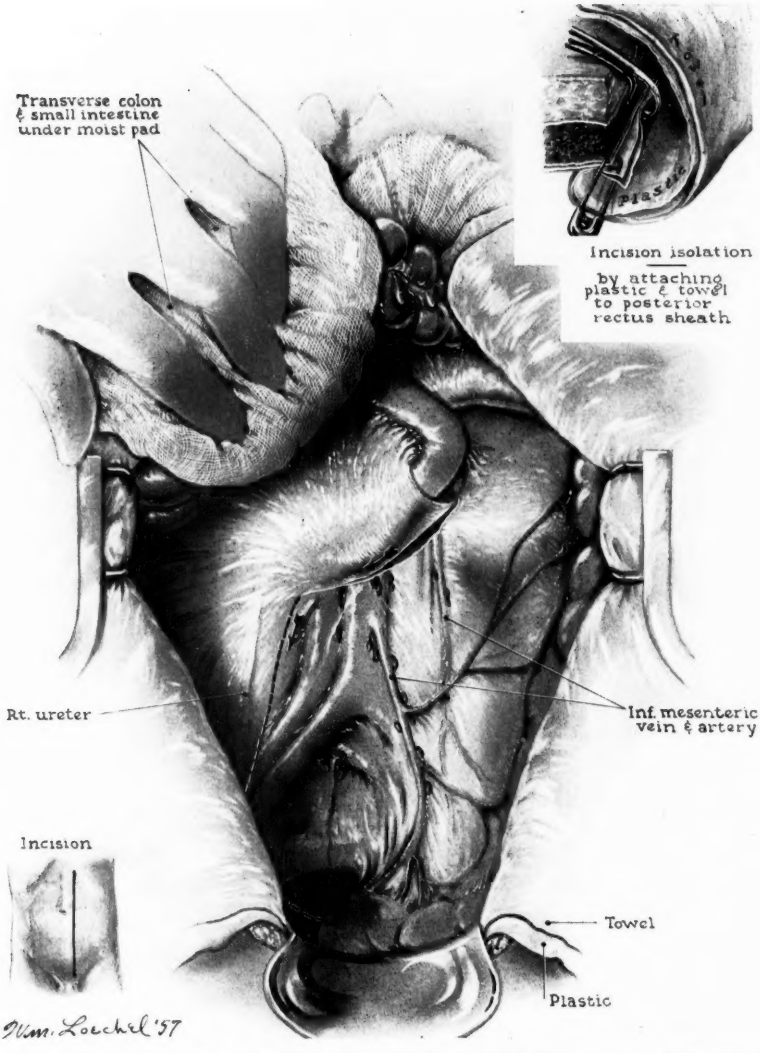

FIG. 1. The abdominal incision and isolation of the incision. The exposure of the vascular-lymphatic mesentery. The initial dissecting incision which enables the surgeon to develop the retroperitoneal dissection and excision of a relatively intact and undisturbed sheet of intramesenteric cancer-bearing tissue.

A Technique for Cancer Isolation and Extended Dissection for Cancer of the Distal Colon and Rectum.—Garnet W. Ault.

A TECHNIQUE FOR CANCER ISOLATION AND EXTENDED DISSECTION FOR CANCER OF THE DISTAL COLON AND RECTUM

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IN A PRELIMINARY REPORT (3) in 1950, evidence was presented that an additional 2 inches, or more, of gland bearing vascular lymphatic tissue could be removed with a specimen of left colonic or rectal cancer if extirpation of the inferior mesenteric artery was done at its aortic origin instead of removing it at the level of ligation suggested by Miles. A series of case reports documented the discussion. A subsequent report on a small series of cases was presented in 1952 (4) and some of the changes in the operative technique were published by Castro in 1956.

The present report concerns our experience with a technique of extended dissection which may be used as an initial "basic dissection" for the removal of cancer in this location. This dissection appears to be more adequate and thorough than the usual standard techniques of dissection. An "in continuity" excision of the retroperitoneal extramesenteric zones of metastases, as advocated by Deddish (10, 11), has been added to the extirpation of the intramesenteric areas of metastases. Although extended dissection may reasonably convince the physician that more cancer and cancer bearing tissue may be removed than may be accomplished by an extirpation of less tissue, it may lead to many unrewarding experiences unless more recognition is accorded to *how* cancer is approached and removed.

The technical and other efforts one should make to isolate the cancer, cancerous tissue, and cancer cells before the actual cancer is removed may be appropriately considered under the term "cancer isolation." Our personal concept at this time begins with choosing the proper location for an adequate abdominal incision. Protection of the incision and early occlusion of the most prominent routes of vascular-lymphatic spread during the initial stages of the operative dissection are the imperative components of the isolation concept. Inferior mesenteric vein and artery ligation should be promptly followed by occlusion of the intraluminal route of spread including occlusion of the marginal vessels. Effort to decrease contact implantation by covering an accessible cancer prior to handling is recommended as an additional step in cancer isolation, if this can be accomplished following the occlusion procedures. It should be recognized that a selective use of any or all of these isolation procedures may be feasible when one is dealing with cancers of the intraperitoneal colon and upper rectum. It must also be conceded that the maximum use of any isolation technique or procedure may be most difficult when removing cancer of the lower infraperitoneal rectum.

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BACKGROUND

Since the introduction of the classical abdominoperineal excision by Miles in 1908, this operation has become established in many countries as (1) the standard operative procedure for removing rectal cancer and (2) the standard by which all other operative procedures are judged. However, one must not forget that the Miles procedure was introduced as a more adequate operation than the existing perineal-sacral methods

TABLE I.—LYMPH NODE METASTASES

Year	*Authors*	*Percentage of cases with involved lymph nodes*
1922	McVay	47
1933	Wood and Wilkie	51
1934	Westhues	59
1935	Gabriel, Dukes, and Bussey	62
1938	Gilchrist and David	68
1940	Coller, Kay, and MacIntyre	64
1943	Seefeld and Bargen	47
1951	Dunning, Jones, and Hazard	57
1952	Grinnell and Hiatt	56

of excision. It was indeed a more adequate operation, but in that same year, 1908, Moynihan presented evidence that lymphatic metastases which may be present at the aortic origin of the inferior mesenteric artery would not be removed by the Miles technique. This challenge to the adequacy of the Miles technique has remained unheeded until recently.

At the turn of the century, the Paul (1892), Block (1902), and Mikulicz (1902) procedures were introduced for removing colonic cancer. These were subsequently modified by the "obstructive resection" of Rankin and Graham. When primary anastomoses seemed feasible, a wedge of mesentery was excised, and segmental excisions were utilized with increasing frequency. The adequacy of exteriorization procedures and wedge-type excisions is now being challenged by the proponents of left hemicolectomy. If this challenge is valid, removal of the inferior mesenteric vascular-lymphatic zone of spread is mandatory when an adequately planned and properly executed left hemicolectomy, anterior resection, or rectal excision is performed. Failure to remove this zone of intramesenteric metastases may designate any excision of cancer of distal colon or rectum as inadequate.

TABLE II.—VENOUS METASTASES

Year	*Authors*	*Percentage of cases with involved veins*
1933	Brown and Warren	61
1941	Coller, Kay, and MacIntyre	15
1943	Seefeld and Bargen	20
1944–1945	Dukes	17
1949	Sunderland	27.6
1950	Grinnell	36
1951	Dunning, Jones, and Hazard	18.6
1954	Barringer and associates	38

THE STATUS OF LYMPHATIC SPREAD

During a 30 year period (1922 to 1952) numerous studies have been made upon the resected specimens of colonic and rectal cancer obtained by standard operative procedures. An incidence of regional lymphatic metastases exceeding 50 per cent is illustrated by Table I (2).

In 1954 Wangensteen and his colleagues demonstrated residual cancer in 43 per cent of patients whose cancer was in the rectum and in 48 per cent of those whose cancer was in the colon. This residual cancer was found in those patients whose initial cancer was a Dukes class C lesion. Most of it was found in lymph node areas at second and subsequent "look" operations. As a result of these investigations, they acknowledged that some of the standard operative procedures were inadequate, and they recommended that the initial operation be more thorough.

These reports on lymphatic spread clearly demonstrate that more than 50 per cent of patients with resectable colonic and rectal cancer will have a Dukes class C lesion by the time they reach the operating room. The supporting evidence that the standard operative procedures now in general use are leaving residual cancer in almost 50 per cent of these patients is most significant. Under these circumstances the conscientious surgeon should be forewarned and forearmed, prior to operation, that a contraction of the field of surgical extirpation would be unpardonable and a continuation of the standard methods of dissection would seem unjustified.

THE STATUS OF VASCULAR SPREAD

During a 16 year period (1938 to 1954) numerous studies have been reported upon the resected specimens of colonic and rectal cancer obtained by the standard operative procedures. An incidence of direct vascular extension or malignant thrombosis exceeding 25 per cent is illustrated by Table II (2).

In 1955 Fisher and Turnbull reported their investigations of freshly resected specimens in which the previously occluded mes-

enteric vessels, adjacent to colorectal cancer, were perfused with saline. Malignant intravascular emboli and cancer cells were recovered from the venous blood and perfusate in 32 per cent of 25 cases of colorectal cancer. These reports demonstrating an incidence of angioinvasive cancer exceeding 25 per cent in both fixed and freshly resected specimens undoubtedly bear a significant relationship to the development of blood-borne metastases. This incidence of angioinvasive cancer should be considered a valid reason for advocating and adopting methods of dissection that will assure early isolation and occlusion of the vascular drainage of the entire resectable area. This should be done prior to the surgical manipulation and handling of the cancer.

THE STATUS OF IMPLANTATION

The existing concern with the complex status of implantation is difficult to evaluate. It is not as clearly documented as the status of either lymphatic or vascular spread.

The transfer of viable cancer cells from the serosal surface of a cancerous colon to peritoneum, viscera, and incisions by sponges, instruments, wash water, or the surgeon's gloves has been demonstrated. The recovery of viable cancer cells from the serosal surface of colonic cancers has been reported in 2 of 20 cases, an incidence of 10 per cent, by Pomeranz and Garlock. In an effort to decrease this form of contact transplantation, they advocated using a gauze colon cover, with occlusive ligatures, to cover accessible cancer as soon as the abdomen is opened and mobilized cancer as promptly as possible.

The relationship between viable exfoliated intracolonic cancer cells and the development of suture line and anastomotic implantation was discussed in 1950 by Morgan, Lloyd-Davies, and Abel. In 1951 Goligher and associates reported a 10 per cent incidence of suture line implantation that occurred in 16 of 152 patients who had sphincter-saving operations performed for cancer of the rectosigmoid and rectum. In 1951 Cole (7) alerted surgeons to this possibility and he subsequently reported a 10 per cent incidence of suture line implantation in 55 patients. Cole and his colleagues have vigorously pursued this problem, and as a result of this and subsequent investigations (8, 9, 19), they have recommended that occlusion of the bowel lumen should be performed, proximal and distal to the cancer, at the beginning of the operation.

A pertinent study of the relationship between suture line implantation and bowel disinfection has been published by Vink. He reported that Brown-Pearce cancer suspension injected within an isolated segment of disinfected rabbit intestine was capable of producing suture line implantation in 12 or 44 per cent of 27 animals. By contrast, suture line implantation developed in only 3 or 13 per cent of 23 animals that did not receive preoperative bowel disinfection. This work merits further study for it indicates that physicians may have to choose between the virulence of intestinal bacteria and the lethal nature of exfoliated viable intracolonic cancer cells. The substitution of carcinomatous peritoneal implantation for bacterial peritonitis, due to gross contamination during operation, should be considered as an important disadvantage of intestinal disinfection.

THE STATUS OF SURGICAL TECHNIQUE

Current surgical literature indicates that many contemporary surgeons have been interested in a more complete extirpation of the intramesenteric vascular-lymphatic zone of metastasis. Excision of the inferior mesenteric artery at its aortic origin, with or without retroperitoneal lymphadenectomy, has been advocated or practiced by Rosi (25, 26), Toupet, Morgan, Lloyd-Davies, Gilchrist, Grinnell (15), Deddish (10, 11), Abel, State, Grinnell and Hiatt (16), Sauer and Bacon, and Welch and Rhinelander.

Extended dissections have demonstrated that the incidence of cancerous intramesenteric lymph nodes, located between the aortic origin of the inferior mesenteric artery

and the Miles level of ligation, may exceed 15 per cent. This is the area Moynihan referred to in 1908. Grinnell and Hiatt (16) reported an incidence of 17 per cent in 1952. Rosi (26) demonstrated positive nodes in 14 to 22 per cent of patients in 1954 and an incidence of 17.8 per cent was reported by McElwain, Bacon, and Trimpi in 1954. These significant demonstrations that more than 15 per cent of patients will have cancerous intramesenteric lymph nodes left in situ if the Miles level of ligation is performed should not remain unheeded.

The complex nature of retroperitoneal extramesenteric lymph node metastasis, in contrast to intramesenteric lymph node metastases, will undoubtedly make this area of spread a most difficult one to study and evaluate. The 1950 report of Deddish (10) demonstrated an incidence of 24 per cent in 25 patients who had abdominopelvic lymphadenectomies. The 1954 report of Sauer and Bacon demonstrated an incidence of approximately 18 per cent in 32 patients subjected to this procedure. It is evident that the addition of retroperitoneal lymphadenectomy to a technique of extended dissection should make it possible to remove more cancer than can be accomplished by standard operative procedures. However, it will require considerable time to assay the value of adding a retroperitoneal in-continuity lymphadenectomy to a technique of extended dissection.

The value of the surgical technique we are using is unknown. However, it represents a conscientious effort to incorporate extended dissection and cancer isolation into a pattern of basic dissection. Upon completion of the basic dissection, the operative procedure may terminate as a left hemicolectomy, a segmental excision, an anterior resection, an abdominoperineal excision or a variety of rectal resections with or without sphincter preservation. In over 800 operations for cancer of the distal colon and rectum, we have used all or parts of this basic technique in 115 instances. Because the approach, isolation, and removal of the cancer, follows a different pattern than we previously reported, a detailed description of the operative technique will be presented.

TECHNIQUE FOR ISOLATION AND BASIC DISSECTION

The abdomen is opened through a left paramedian incision extending from the symphysis pubes to within 1 or 2 inches of the costal margin (Fig. 1). Complete isolation of the incision is accomplished by covering its edges with a thin towel placed over a sheet of plastic or rubber. Adequate exposure is obtained to assure immediate complete examination of all abdominal contents from the esophageal hiatus to the pelvis. Most of the transverse colon and small intestine are then displaced outside of the abdomen and are spread out on the epigastric and right abdominal surface. They are covered with warm moist pads and held in place by an assistant who must not cause mesenteric traction and angulation along the edges of the incision. This initial maneuver permits clear visualization of the entire left colon and upper rectum. The vascular lymphatic mesentery is adequately exposed and accessible. Cancer handling and mobilization is to be avoided at this time. The initial dissecting incision starts at the duodenojejunal angle and the peritoneum is opened across the lower border of the duodenum as far as the right edge of the vena cava. Elevation of the duodenum and a variable portion of the pancreas in a cephalad direction will permit exposure of the left renal vein (Fig. 2). Near the duodenojejunal junction the large inferior mesenteric vein will be exposed in its cephalad and medialward course to join the splenic vein. It should be clamped, cut, and ligated either at the level of the left renal vein or near where it joins the splenic vein. Lymph nodes in this area should be removed in continuity with the specimen. The main route of vascular malignant embolism is thus *occluded at the beginning of the operation.* From this stage until near the end of the operation, the dissection is almost en-

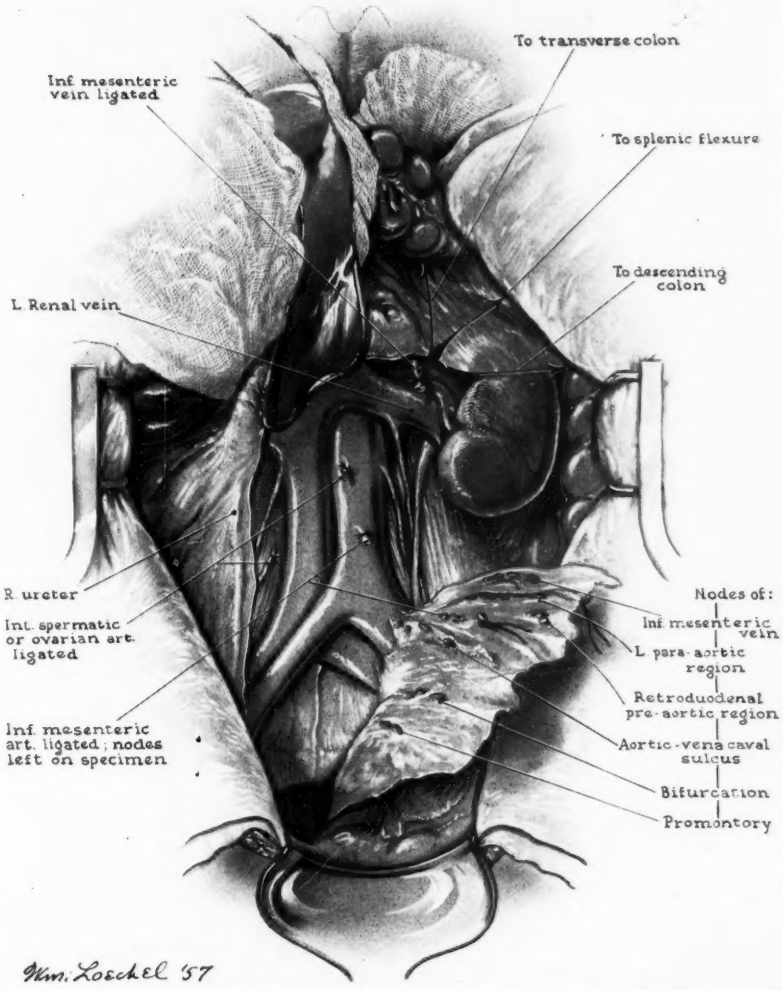

FIG. 2. The exposure of the left renal vein. The early ligation of the inferior mesenteric vein. The excision of the inferior mesenteric artery at its aortic origin. The incontinuity retroperitoneal lymphadenectomy combined with mesenteric excision. The lines of extension of the dissection to the upper descending colon, splenic flexure, or transverse colon. The dissection of the tissues and mesentery proceeding from a distance toward the cancer. The basic dissection.

tirely retroperitoneal. Sharp scissor dissection is then started at the level of the left renal vein so that retroduodenal, preaortic, left para-aortic and aortic-vena cava lymphatics are removed in continuity. This retroperitoneal dissection continues in a caudal direction to the aortic origin of the inferior mesenteric artery. This is located at

an average distance of 3.75 centimeters cephalad to the aortic bifurcation.

The variable distance is 2 to 6 centimeters. The inferior mesenteric artery is suture tied with black silk flush on the aorta and the ligature on the specimen side is cut 1 inch long for future identification. During the dissection from the left renal vein to the inferior mesenteric artery, ovarian or spermatic vessels may require ligation and division in order to facilitate the dissection. The oozing from small arteries and veins in the perivascular tissue of the aorta and vena cava may be adequately controlled by placing a warm moist pressure pad over their exposed surfaces. Because it is possible for the marginal vessels to act as a vascular shunt between the middle colic vessels and the middle and external hemorrhoidal vessels, occlusion of the marginal vessels is carried out next. A special colon clamp (Figs. 3 and 4) is used to occlude both the lumen of the colon and the marginal vessels. Whenever it is possible to do so, this is placed 10 centimeters or more cephalad to the cancer. *The cancer is not handled or mobilized.* When it is feasible to do so, the clamp is placed across the colon or upper rectum 10 centimeters (or an acceptable distance) caudal to the cancer. Placing the clamp caudal to a cancer of the upper rectum may have to be delayed until after the gauze pad is removed from the ventral surface of the aorta and vena cava and the retroperitoneal dissection is continued in a caudal direction to the origins of the hypogastric vessels. Bifurcation and promontory lymphatics (Fig. 2) are included in the specimen as the presacral space is entered, and the ventral surface of the sacrum is exposed. The dissection may be facilitated if the right ureter and spermatic or ovarian vessels are left on the peritoneal flap that is elevated to the right and parallel to the vena cava (Figs. 2 and 3). Careful, slow, and deliberate dissection will be necessary in exposing the left ureter and spermatic or ovarian vessels. This is done so as to leave the left ureter undisturbed in its normal position (Fig. 2). A normal ureteral blood supply is thus assured. Left para-aortic lymphadenectomy in continuity is performed from the left renal hilus to the left common iliac vessels. The left ovarian or spermatic vessels may be removed in continuity with the specimen, or they may be left *in situ*.

With the completion of this basic extended dissection, preceded by the early isolation and occlusion of the vascular, lymphatic, and intracolonic routes of spread, the cancer may be gently covered with a sterile face mask. The tapes are brought through an avascular area in the mesentery and are gently tied by the operating surgeon. Tape occlusion is not necessary if the clamps have been applied earlier.

This basic dissection may be extended in a cephalad direction to the splenic flexure or to include the mesentery of the left transverse colon (Figs. 2 and 3), or it may be extended in a caudal direction to the superior surface of the levator ani. The subsequent dissection, which may be added to this basic extended dissection, will be facilitated by the basic dissection. The termination of the operative procedure as a left hemicolectomy, anterior resection, or rectal excision should be determined by the location of the cancer.

EXPERIENCE AND COMMENTS

In the first 1940 to 1950 group of dissections, Table III, an approach from the sacral promontory toward the inferior mesenteric artery was used (3). This was considered unsatisfactory. During the period from 1951 to 1952 the dissections were started at the lower border of the duodenum so that the main routes of vascular-lymphatic spread could be occluded during the initial stages of the dissection. However, it soon became more evident that a low position of the duodenum and pancreas in some patients not only crowded the field (4) but an inadequate amount of vascular-lymphatic tissue would be excised under these circumstances. Therefore, since our

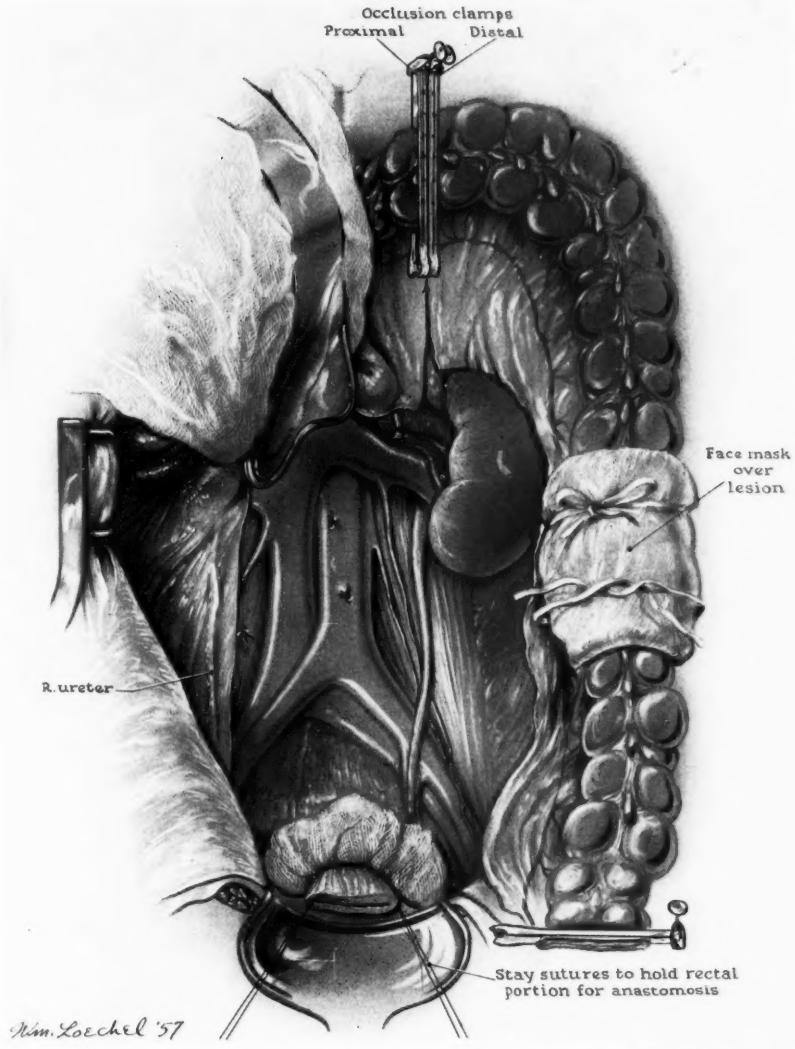

FIG. 3. The occluded bowel lumen and marginal vessels. The relatively undisturbed covered cancer with its intramesenteric metastases is almost ready for removal from the abdomen.

1952 report (4), the level of extirpation of tissue has been extended to the level of the left renal vein whenever this seemed feasible. Attempts to extend the dissection cephalad to the left renal vein have been unrewarding. The initial dissecting incision (Fig. 1) permits the surgeon to elevate the duodenum and pancreas and to expose the left renal vein. Exposure and ligation of the inferior mesenteric vein at this height and at this time are considered an effective means of preventing malignant intravas-

TABLE III

	Year	I.M.A.* excision cephalad to left colic	I.M.A. excision at aortic origin	Dissection from lower border of duodenum	Dissection from left renal vein	Operation terminated as: Abdomino-perineal	Anterior resection	Left hemicolectomy	Pull-through	Swenson	Sacral anastomosis
Group I	1940		1			1					
	1941	1	1			2					
	1942–1946	Investigation incomplete during war years.									
	1947	5				3			2		
	1948	8	2			7	2		1		
	1949		3			1	2				
	1950	6	3			2	6	1			
Group II	1951	3	3	1	1	4	4				
	1952	3	6		2	4	5	2			
Group III	1953	3	9	7	1	6	11	2	1		
	1954	4	2	3	7	6	8	1		1	
	1955	1		6	9	4	9	2			1
	1956	1	4	2	7	4	6	4			
Total		35	34	19	27	44	53	12	4	1	1

Table III indicates that the work progressed through 3 overlapping periods of investigative dissection, and these 115 dissections terminated as tabulated.
*Inferior mesenteric artery.

cular emboli from reaching the liver. This exposure facilitates the development of an excellent retroperitoneal fascial plane of dissection so that a large sheet of retroperitoneal extramesenteric and intramesenteric tissue enclosing intact lymph channels, nodes, and blood vessels may be removed in continuity (Fig. 4). A minimal amount of cutting through, across, or into areas of metastases is achieved by this technical approach.

In the early dissections the chain of 3 to 5 aortic-vena caval nodes, located between the aorta and vena cava, were not removed in continuity (Fig. 2). These are now removed in continuity with the specimen. During excision of this lymphatic chain, chylous fluid has occasionally been observed exuding from the severed caudal radicles of the cisterna chyli. Under these circumstances it has seemed prudent to separate the aorta and vena cava and suture the area with mattress sutures. This method should decrease the risk of subsequent leakage of chylous fluid.

As the supporting fascia is being removed from the ventral and lateral surfaces of the vena cava and aorta, the vena cava will gradually become dilated. To our knowledge, this has not been followed by any deleterious effects. In the area between the aortic bifurcation and the sacral promontory, the vena cava will often be held rather firmly in fascial planes. If malignant bifurcation nodes involve this fascia or the vena cava, their removal may require excision of a portion of the vena cava. The removal of promontory nodes caudal to this area is rarely a difficult procedure.

The left ureter is frequently exposed, but undisturbed, from the level of the renal pelvis to the brim of the pelvis. This exposure facilitates the left para-aortic lymphadenectomy when this procedure seems indicated. In some instances it is possible to remove a strip of tissue 1 to 1½ centimeters wide and 8 to 10 centimeters long containing lymph nodes and channels. Whether this will be a rewarding extirpation or not will undoubtedly depend upon the selection of the case and the technique of the surgeon. During this dissection some of the left lumbar arteries and veins may be exposed and suture ligation will be necessary to control bleeding.

The writer's experience with the occlusion clamp has been most satisfactory when it has been applied to accessible mobile colon or upper rectum. One pair of the clamps may be removed with the specimen (Fig. 4). One clamp may be left on the end of the colon and the one on the lower

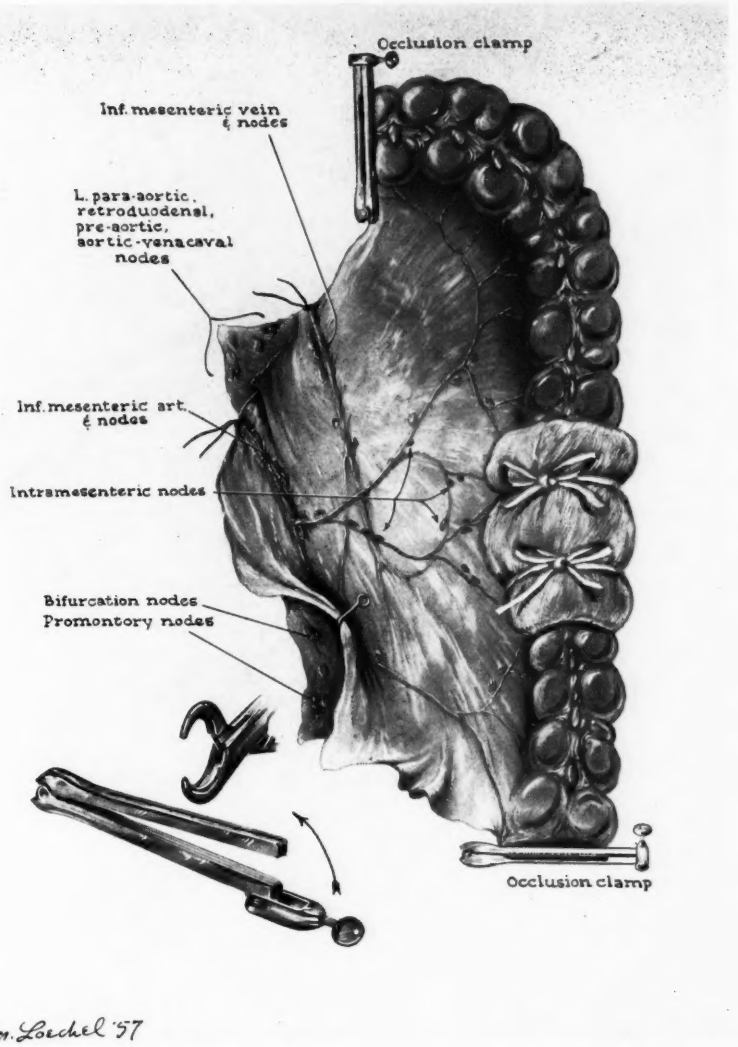

FIG. 4. The specimen. The large sheet of intact mesentery containing the undisturbed blood vessels and lymphatics which may contain angioinvasive and lymphogenous cancer illustrates the goal of the basic dissection. The occlusion clamps are a modification of the original clamp designed by Harvey Stone.

rectum may be cut off after the stay sutures have been inserted through the lateral mesorectum to elevate and hold the rectum in position for anastomoses (Fig. 3). When the blade lock is set properly, the clamps will not spring open, and gross soiling is thus avoided. Under some circumstances it may be difficult or impossible to apply the clamps prior to manipulation or handling the cancer, and their use under these cir-

cumstances becomes a more elective procedure.

No instances of inadequate blood supply to the lower rectal segment have been encountered, regardless of whether the middle hemorrhoidal vessels were sacrificed or left intact. The external hemorrhoidal vessels have been found capable of maintaining an adequate blood supply to at least 15 centimeters of the rectum—as measured from the external anal margin. Proof of the functional capabilities of the marginal artery may be demonstrated if it is cut and bleeding occurs. Viable proximal colon for anastomoses or colostomy has been obtained for all operative procedures to date.

This wide retroperitoneal dissection, accompanied by the removal of a large amount of mesenteric tissue, has facilitated mobilization and removal of many cancers which remained untouched until the specimen was lifted out of the abdomen. The removal of cancers of the flexure areas and those in the descending colon is facilitated by this surgical approach for they may be handled after these isolation and occlusion procedures have been carried out.

One of the most rewarding experiences has been the examination of the fresh specimen prior to fixation and further study (Fig. 4). If a good retroperitoneal fascial plane has been followed, the intramesenteric blood vessels and lymphatics will be enclosed within a sheet of tissue covered by peritoneum on its ventral surface. If the ligatures on the inferior mesenteric vein and artery are held in clamps and the mesentery is spread out in its normal configuration, one may clearly demonstrate the rather complete removal of the mesentery with the undisturbed blood vessels and lymphatics contained therein. Cancer cell seeding should be materially decreased for a minimal amount of cutting through, across, or into zones of spread has been done at the cephalad portion of the specimen.

Peritonealization of the uncovered area has not been a problem when the operation terminated as an anastomotic procedure. A sheet of mesentery from the upper descending colon or the transverse mesocolon can usually be brought down to, or beyond, the bifurcation area, and it may be sewn to the cut edge of the peritoneum from the duodenojejunal junction to the depths of the right pelvis.

Before presenting a table of experience, it would seem appropriate to state that it would be most unfortunate if this operative method were considered as an acceptable "routine operative procedure." It is not a "routine procedure," but it is a more adequate cancer operation for selected cases. In over 800 operations for cancer, its use was found to be justified for slightly more than 100 patients. With increasing skill and judgment, we hope to use the method more frequently. However, this much dissection materially increases the operative time, and this fact should be given consideration. Obesity, which increases the technical difficulty of performance, has been a contraindication to this much dissection.

Table III indicates that, following the dissection, the operative procedure terminated in a variable manner. This observation is the correct interpretation, for this dissection is basic and the termination of the operation is dictated by the location of the lesion.

SUMMARY

1. A concept of cancer isolation and basic extended dissection has been presented.

2. Some of the background for the current dissatisfaction with the standard methods of removing cancer of the distal colon and rectum has been reviewed.

3. The status of lymphatic, vascular, and implantation spread has been outlined.

4. Some 15 years of investigative work has been supplemented by the recorded experience and recommendations of contemporary surgeons in developing a technique for cancer isolation and basic extended dissection.

5. An experience with the selective use of this surgical procedure for 115 patients has clearly demonstrated that *how* the cancer is

approached and removed is most important. The early occlusion of the routes of vascular-lymphatic spread, the isolation of the cancer, and the opportunity to remove relatively undisturbed intramesenteric areas of metastases by the retroperitoneal dissection represent a conscientious effort to decrease the incidence of intravascular dissemination and local implantation.

6. The value of the rather complete extirpation of undisturbed intramesenteric metastases is not proved, but the merit of doing so warrants further study. The value of the retroperitoneal lymphadenectomy will be most difficult to assess for the handling of cancerous retroperitoneal lymphatics may be followed by an increase in cancer cell dissemination.

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ANALYSIS OF 2,514 EXAMINATIONS DURING EARLY PHASES OF AN X-RAY SURVEY OF THE BREAST

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IF A UNIVERSAL CANCER TEST were to be announced tomorrow, the necessity of finding the lesion would only aggravate the present problem of early cancer detection. As matters now stand, cancer of the breast usually is first discovered by the patient herself. Since a so-called small lesion, 1 centimeter in diameter, already has gone through possibly 30 of its 40 life cycle doublings, teaching the patients to make self examinations can hardly improve the situation. It is obvious that some other means must be sought to discover early breast cancer if modern surgery and radiation therapy are to be lifted from their present static level of effectiveness. These are some reasons why roentgenographic screening of the breasts of presumably healthy asymptomatic women was initiated by us in February 1956.

Periodic re-examinations at 6 month intervals are planned for this group of women during the next 10 years. Besides the detection of early cancer, we plan to study the physiologic changes of the normal breast and the relationship of mammary dysplasia to cancer.

This progress report summarizes our experience of the first 16 months of operation. Methods for selection of volunteers for the project and its mode of operation have been described elsewhere (1, 2).

Of the 2,514 examinations of the breast which were done on 1,291 asymptomatic women, 1,033 were second examinations 6 months after the first and 190 were third examinations 12 months after the first study.

Forty-four of these women were operated on because of the x-ray findings. Of these, the presence of cancer was questioned by the roentgenologist in 25 cases. In 2 of these cancers were definitely reported by the roentgenologist, and the diagnoses were confirmed by the pathologist. In the other 23 cases, cancer was found in 3 cases. In 3 of the 5 cancer cases—the lesion in all but 1 under 1 centimeter in diameter—axillary metastasis already was present. And in the remaining 20 cases, the pathologist reported the presence of 2 "precancerous lesions," 3 fibroadenomas, 2 inflamed cysts, 2 sclerosing adenomas, 4 cases of intraductal hyperplasia, and 7 negative cases. In the 7 cases, the roentgenologist found that the surgeon had failed to remove the suspected lesion. Naturally, these patients will receive special attention with more frequent follow-up examinations.

In the group of 44 patients who underwent diagnostic resections, 19 benign lesions were reported by the roentgenologist and all were confirmed by the pathologist. One case was reported as negative by the roentgenologist, but the surgeon thought he felt a lump which required resection and study. The diagnosis made by the pathologist was normal breast tissue. Of the other 18, two were diagnosed as intraductal hyperplasia and the rest as either adenosis with small cysts or fibroadenoma (Table I).

A summary of the x-ray findings is found in Table II. Malignancy was suspected or diagnosed by the radiologist in 2 per cent of all x-ray examinations. Approximately 27 per cent were reported as negative and 70 per cent as breasts with benign or dys-

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TABLE I.—FINDINGS IN 44 PATIENTS OPERATED ON FOLLOWING X-RAY EXAMINATION

		Operation findings			
X-ray report	*No. of operations*	*No confirmation (Lesion not removed)**	*Benign*	*"Precancerous"*	*Carcinoma*
Negative	1	–	1	0	0
Benign	9	–	9	0	0
Probably benign	9	–	9	0	0
Possibly malignant	23	7	11	2	3
Carcinoma	2	0	0	0	2
Totals	44	7	30	2	5

*As shown by subsequent x-ray examination.

plastic lesions. The frequent diagnosis of dysplasia may have resulted from the presence of a high proportion of women who joined this survey group because they were conscious of lumpy breasts or had a history of previous surgery for benign lesions. Also there was a purposeful tendency by the roentgenologist to over-read the films.

DISCUSSION

As a rule the response of women and physicians to our pilot survey has been enthusiastic and confirms our impression that a real need exists for this type of examination. Although no patient with a dominant or outstanding breast mass was admitted to the survey, a number of our volunteers were women with diffusely nodular or intermittently painful breasts. Many with a history of benign dysplasias or a record of several operations for benign lesions were referred by their physicians who found our reports a valuable aid to their own periodic clinical evaluations. Co-operation of this type is most desirable since it gives the patient the benefit of our method of tumor detection and necessitates periodic review by the patient's physician. All 5 patients whose neoplasms were detected in our survey had been examined by their physicians within the preceding 3 months and had been considered free of breast tumors.

Close contact with the family physician has provided us with essential information such as operative findings and notes on other forms of concomitant therapy. More important, direct reporting to the physician has resulted in prompt treatment or close clinical follow-up of lesions suspected by the radiologist of being premalignant or malignant. Since more diagnostic resections should result from this approach and since these operations will be done on patients before the onset of clinical symptoms, more early cancers should be found.

In the majority of cases periodic x-ray examination reassures the patient, who often is seriously worried about a real or imaginary "cystic" condition. But at least 11 volunteers have refused to return for re-examination because they were emotionally disturbed by the procedure. Unquestionably a number of women are unable to withstand the strain of a periodic check-up of this type, especially since it involves a certain time lag (usually a week) between examination and report.

Many of our long term goals will not be achieved for a number of years. Our findings are concerned with new criteria for the differential x-ray diagnosis of breast lesions in the absence of clinical symptoms. Valuable knowledge was gained by re-evaluation of the 2 cancers, diagnosis of which was missed on first x-ray examination. Since both tumors could be clearly visualized on the original x-ray film, much was learned about the roentgen appearance of "early" breast cancer. This type of retrospection by using early film records may be expected to

TABLE II.—X-RAY REPORTS IN 2,514 EXAMINATIONS OF 1,291 ASYMPTOMATIC WOMEN

X-ray report	*No. of patients*	*Per cent*
Negative	688	27.4
Benign	1691	70.4
Probably benign*	80	
Possibly malignant	49	2.2
Carcinoma	6	
Totals	2514	100.0

*Includes cases in which a lesion was incompletely visualized in a dense dysplastic breast. Clinical evaluation and close roentgen follow-up were suggested.

yield even more information over the years. Of equal interest will be close follow-up of those patients for whom clinicians believed that surgery was not indicated in spite of suspicious roentgen findings.

SUMMARY

Preliminary results of 2,514 periodic examinations of the breast of 1,291 asymptomatic women are reported. Forty-four patients were operated on because of the x-ray findings. In 25 cases, the roentgenologist reported the presence of cancer in 2 and a lesion suspicious of cancer in 23. Five cancers were actually found in this group and confirmed by the pathologist. All lesions but 1 were less than 1 centimeter in diameter, yet 3 of them had already metastasized to the axilla. In the remainder, the lesions described by the pathologist were: "precancers" (2), fibroadenomas (3), inflamed cysts (2), sclerosing adenosis (2), intraductal hyperplasia (4); in the remaining 7 cases, the surgeon failed to remove the lesion and these patients are to be re-examined periodically.

Of the 19 patients reported to have benign lesions in the breast, the x-ray diagnosis was confirmed in every case.

On the basis of the present preliminary findings it is believed that x-ray screening merits further study for the detection of nonpalpable clinical asymptomatic mammary cancer. The experience gained by long term periodic check on all changing patterns of the normal breast should go far in setting standards for the detection of earlier neoplastic changes in the breast.

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EDITORIALS

THE SELECTION OF PATIENTS FOR RHINOPLASTY

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OWING TO INNUMERABLE ARTICLES on cosmetic plastic surgery in newspapers and in periodicals for lay consumption, there is an ever increasing number of persons who are making a critical inspection of their features and are becoming especially conscious of congenital and acquired defects affecting the supportive structures of the nose. Particular reference is being made here to humped, crooked, hooked, or depressed noses with or without a drooped or bulbous nasal tip. Since people are being made aware of the possibilities of corrective rhinoplastic operations in which surgical alterations are made in the bony and cartilaginous framework of the nose, it is not surprising that more and more individuals are requesting information from their local physicians concerning the advisability of this type of operation. If a physician who has had no training in plastic surgery is to give competent advice, it is important for him to realize that not every person with a nasal defect is a fit candidate for rhinoplastic surgery. Furthermore, if such surgery is going to bring satisfying results, the surgeon cannot promise precise postoperative results to suit the fancy of each patient because such exacting esthetic effects cannot always be surgically achieved. However, properly selected patients who are informed of the facts are not going to expect too much or the impossible and, with few exceptions, are going to be pleased with the end results even though some small imperfections may be present.

Since the psychologic benefits derived from cosmetic nasal operations have been thoroughly substantiated in recent years, there is no need in citing cases to justify this type of surgery. Many stable and well integrated persons can be embarrassed, self-conscious or sensitive about a nasal deformity, and it is certainly most gratifying to observe the satisfaction which such people experience following a successful rhinoplasty; as a matter of fact, one not infrequently can detect agreeable personality changes in these patients following alterations in nasal contour. In contrast to such individuals, there are, unfortunately, many people with psychopathic tendencies and neurotic attitudes who never would be satisfied with the results of any rhinoplastic procedure even though the defective nose is changed to one of ideal proportions.

People who request cosmetic nasal operations can be divided into two categories: those who will benefit by this type of surgery and those on whom a plastic surgeon for various reasons should refuse to operate.

The first group involves men and women each of whom has a nasal deformity and is desirous of undergoing corrective nasal surgery merely for the sake of improving his facial appearance. Such an individual may be self-conscious or sensitive about anatomic irregularities of his nose but looks for nothing other than improved nasal contour from a

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plastic operation. As will be pointed out later, there are some human beings who expect all sorts of extraneous problems to be solved by rhinoplasty. While the type of person being discussed here may have some definite opinions concerning his ideas of esthetic nasal proportions, he has no overly precise notions in regard to the surgical alterations which should be made on his own nose. On the contrary, he leaves it to the discretion of the surgeon to determine what changes are necessary and can comprehend the fact that the end results of the operation may not be completely faultless. In short, he is the sort of person who invariably is pleased following a successful rhinoplastic procedure.

In contrast to this first group of people, there is a smaller group of individuals with mental and emotional problems, the cause of which they ascribe to some real or imaginary nasal defect. The actual reasons for such disturbances are not apparent to them but are buried in a mire of inner conflicts and emotional upheavals. To such a person, the nasal deformity looms as the only cause for his depressing and insurmountable problems which interfere with emotional outlook and social acceptance. It seems to him that a corrective nasal operation would give him an immediate sense of relief, well-being, and self-confidence. Nothing, of course, is farther from the truth. On the contrary, the patient finds after rhinoplasty that his emotional pattern continues along the same old lines, with no relief from inner conflicts and no increase in self-esteem. He usually is left disgruntled, disturbed, and dissatisfied with every phase (including the financial aspect) of the rhinoplastic procedure.

Some psychopathic individuals with paranoid tendencies have the ridiculous notion that everyone is laughing and talking about their nasal defect which, in reality, may be very minor in character. A rhinoplasty in such cases solves nothing and may lead the surgeon into countless difficulties of an unpleasant nature.

It is even more distressing for the unsuspecting surgeon to go ahead with a rhinoplasty on a person with an undiagnosed psychosis who seems entirely normal before operation but postoperatively reveals unmistakable evidence of his distorted mind, often being absurdly displeased with a really satisfactory operative result.

It is perfectly true that some professional actors, models, and other persons in public life may find it advantageous for their careers to undergo a corrective nasal operation. However, when the individual is educationally unprepared or psychologically unfit for his chosen occupation, no form of rhinoplasty is going to bring vocational success no matter how pronounced his nasal deformity may be. When a patient explains that his entire career hinges on the success or failure of a nasal plastic operation, no experienced plastic surgeon will have any desire to assume such unreasonable responsibilities. In such cases, the patient seems to lack insight into the fact that a well proportioned nose is not the only passport needed to obtain the job or the social life of his dreams. A nicely contoured nose is no guarantee for outstanding success in any field of endeavor.

Not infrequently, the plastic surgeon encounters individuals with a deep seated sense of inferiority who attribute all of their feelings of inadequacy to some deformity of the nose. Often such persons are of the opinion that a rhinoplasty would give them immediate self-confidence and solve all of their problems. However, such is never the case. Unless the patient can attain inner security and self-esteem through psychiatric assistance, a nasal plastic operation never should be recommended.

Other people on whom a rhinoplasty is better avoided are those who believe that a change in nasal contour would improve their features so much that an unfaithful marriage partner or an indifferent lover would take renewed interest in them, thereby avoiding the probability of a divorce or broken love affair. Shattered romances, disillusionment in marriage, and unsatis-

factory social existence are among life's difficulties never solved by altering the contour of a nose.

Too often the discussion of a nasal plastic operation between surgeon and patient will lead the latter to anticipate a specific type of postoperative result. If the patient is permitted to choose from stock photographs the type of nose which is most appealing to him and then is encouraged to assume that his nose can be modified to similar proportions, he is likely to be disappointed with the end results of the rhinoplasty because such precise results can by no means always be attained.

Some people with a nasal deformity go to the extreme of having a plaster cast of their nose prepared after which they remodel the nose in clay to suit their fancy. The clay model then is presented to the surgeon with instructions to modify the patient's nose to correspond. As previously mentioned, such exacting requests are seldom surgically fulfilled. If the patient is given the assurance that such results can be achieved, he is rarely pleased with the operative result.

Particularly distressing to the plastic surgeon is the individual who exhibits a picture of some person he admires and expresses the desire to have his nose altered to resemble that in the picture. Not only is it impossible to make one nose entirely similar to another, but too often such a person goes through mental fantasies imagining that rhinoplasty will modify not only his nose but his whole face as well so as to resemble the person he regards with approval. In almost every instance, the patient after the surgical procedure is deeply dissatisfied to find that, in spite of a good operative result, he still looks just like himself. Many a young woman desires a rhinoplasty in the unrealistic hope that her secret reveries will come true but is in for bitter disappointment when she finds that her reconstructed nose has not turned her into a scintillating beauty nor has it brought a dashing suitor to her door.

After a rhinoplastic operation, every patient examines his nose critically and is displeased if the contour does not resemble that which was proposed and promised by the surgeon. A patient who is to have a rhinoplasty should be told that the appearance of his nose will be improved but that the exact contour cannot be predetermined. Furthermore, he should be informed that a nose, no matter how perfectly modified during an operation, may unavoidably undergo some distortion during the healing period, and that scar tissue may possibly change the shape of the nose further during the months to follow. If flaws do develop, it occasionally is necessary to perform a secondary operation. However, a patient thus informed of the truth is not going to expect something which was never promised.

In conclusion, I should like to emphasize the fact that any person who is to undergo a corrective nasal operation may be given reasonable assurance that the contour of his nose will be made more pleasing and attractive if the operation is performed by a competent surgeon. There is no question but that countless individuals have been made happy by nasal plastic procedures. However, if the patient expects a rhinoplasty to do anything more than alter the shape of his nose, he had better be discouraged from even thinking about this type of cosmetic surgery.

THE "UNIQUE" SURGEON

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A MATURE PERSON thinks of the immediate in terms of the ultimate. This is the basis of good living principles and sound surgical judgment. The present, or the immediate, has too often proved itself a jailer of our minds. It holds us captive. We live under the tyranny of a present incident and for this reason may react at times in very immature ways. A surgeon should have the bearing of maturity, and one way of achieving this maturity is to think of the immediate situation in terms of the ultimate goal.

Martin Buber has said, "The foremost task of every man is to bring into actuality his unique, unprecedented, never recurring potentialities." This is good personal philosophy. Each of us is a unique personality and because of this we bring to every problem our individual and particular facet of approach. No two persons can ever make exactly the same contribution to the same problem. This is the gift of individualism.

The evaluation of the immediate in terms of the ultimate is analogous to the performances of a thermometer and a thermostat. The function of a thermometer is merely to rise or fall according to the immediate. It reflects with reasonable accuracy the "temperature" of the present. Not so the thermostat. The thermostat responds to the present in terms of the ultimate. It is constantly releasing energies to change things from what they are to what they ought to be. The skill of the surgeon should be exercised in a like manner, because the resultant forward thinking cannot help but serve the best interests of the patient.

A surgeon must know his true worth and value. He must confront his immediate problem with the ultimate objective of bringing his full potential into actuality. This is the mark of a "unique" surgeon, and it is to be hoped that through the co-operation of these "unique" surgeons we shall be able to solve more quickly and more effectively some of our most distressing and frustrating problems.

THE SURGEON AT WORK

PREVENTION OF MASSIVE HEMORRHAGE SECONDARY TO HEMORRHOIDECTOMY

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MASSIVE HEMORRHAGE secondary to hemorrhoidectomy is an emergency of the first order. Potentialities for fatal outcome following minor surgery, its impelling urgency aggravated by large blood loss into the rectum before detection, and the surgeon's helplessness in prevention combine to make it of major importance. All of these aspects have been discussed in the literature except the most important one—how to prevent it. On this point we have been unable to find a single useful suggestion.

For the patient such hemorrhage is a frightening ordeal. He has usually returned home in retrospection of what is commonly regarded as minor surgery with the logical assumption that all was well. Suddenly there is an explosive gush of blood clots, a confused midnight rush to the hospital, a second visit to the operating room, and blood transfusions, all of more concern than the original surgery. For all of this the patient may or may not have been forewarned.

During the past several years we have had a unique opportunity of observing the slowly unfolding process of intra-anal wound repair in relation to secondary bleeding. These observations have now revealed sufficient information to serve as a sound basis for preventive measures.

INCIDENCE

There are such incredible variations of incidence gathered from various sources as to make even approximation inconclusive. Some of this discrepancy is explainable without searching too deeply beneath the surface. But beyond that, just what is one to believe when some proctologists profess never to have encountered a single instance while to others it is of such frequency as to be a source of ever present concern?

To us personally, its significance lies not in the exactness of any numerical figure but in the fact that it is the one circumstance above all else in proctologic surgery wherein even brief loss of contact with competent medical assistance could spell disaster. Whatever the incidence and whatever one's experience in the past, the potentialities for serious surgical and medicolegal consequences are incontrovertible and deserving of study.

POSTOPERATIVE HEMORRHAGES

Clear distinction should be made between hemorrhage occurring during the first several postoperative days and that occurring during the second week. The former occurs while the patient is still in the hospital which eliminates the difficulties associated with re-entrance. It is due to insecurity of the ligatures which might be ascribable to fault. But the early postoperative hemorrhage does not constitute the important problem either in incidence or seriousness.

The delayed hemorrhage of which we particularly speak occurs during the second week and has nothing to do with the effectiveness of hemostasis achieved at operation. In observations to be described we have verified the day by day fate of intra-anal ligatures. Invariably they are so loose by the third day, no matter what the material used, as to be wholly ineffectual. It should thus be obvious that hemorrhage occurring 7 to 12 days later could not conceivably have connection with ligatures or sutures placed at operation. Indeed, passage of ligatures is frequently observed by patients before they are

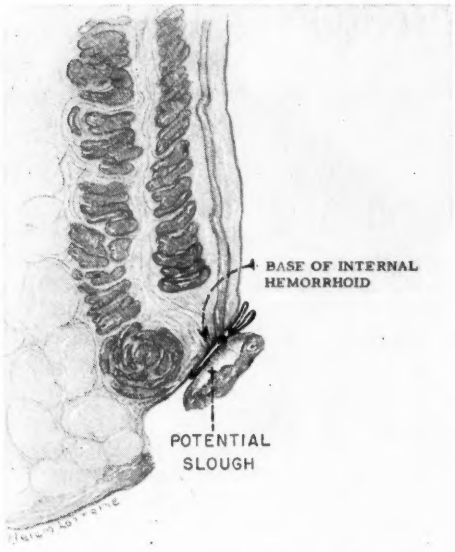

FIG. 1. Strangulated stump following ligature method. As typically performed this procedure involves not only a comparatively large amount of undissected tissue to be ligated but also its concentration at the one area within the single ligature. The result is a relatively large slough with commensurate tendency toward secondary hemorrhage.

discharged from the hospital, long before secondary bleeding.

One other fact is worthy of note here. It seemed significant that, although most postoperative wounds in the area are continuous from within to outside the sphincter, massive bleeding originates only on the inside and in spite of the fact that all parts of the wound are soiled by the same stool contaminants and components. This evidence tends to rule out infection alone as the principal causative factor.

OBSERVATIONS OF HEALING WOUNDS

Several years ago we described an office procedure for the ligation of internal hemorrhoids with special instruments. Basically it comprised the standard ligature method of hemorrhoidectomy with the important difference that application was strictly limited to internal hemorrhoids. Such restriction renders this office technique possible because the area of the internal hemorrhoids is, of course, wholly insensitive. This treatment was devised for a class of patients whose sole symptom was bleeding due to internal hemorrhoids and without other significant disease. The circumstances are often less than would seem to justify hospital surgery and yet more than temporary relief offered by alternative injection treatments would satisfy. The method has proved to be a simple and satisfactory solution because of actual destruction of pathologic tissue intentionally deprived of blood supply (Fig. 3).

The same insensitivity which brought remedial surgery within the scope of an office procedure also made readily feasible day by day anoscopic observations. This was a new and unexplored opportunity for painless and close observations never within practical reach after hospital operation.

These ligations performed as an office procedure reached their maximum effect in producing areas of tissue sloughing, and our anoscopic observations at frequent intervals showed the whole process from beginning to end. An unexpected reward was the discovery of what we believe to be the predominant and preventable cause of secondary bleeding from intra-anal wounds.

Early in our experience with the office procedure we were confronted by secondary hemorrhage in disturbing incidence and severity. This, of course, was evidence of the effectiveness of the

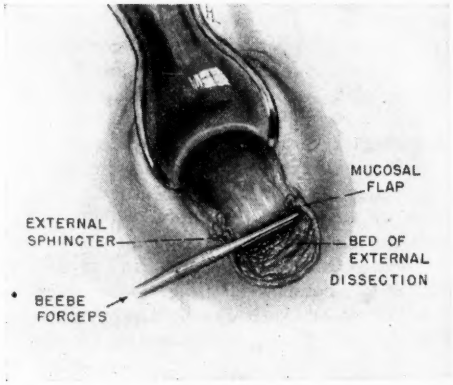

FIG. 2. Alternative pattern of hemorrhoidectomy which has several advantages over the ligature operation as far as sloughing and its effect on secondary hemorrhage are concerned. The Beebe forceps is ideal for the purpose illustrated. It has longitudinal striations and narrow blades. In keeping with the objectives mentioned, the distal edge of mucosa should be severed close to the forceps and the mattress sutures likewise placed as close as possible.

method but, at the same time, a source of understandable concern. Such incidents were not nearly so serious as those following hospital surgery because it was a simple matter, at the office, to place a hemostatic ligature without any anesthetic whatsoever. Nevertheless, occasions might be too inopportune and the circumstances too disturbing to warrant satisfied complacence.

Fortunately, this problem was successfully resolved. The key to the situation proved to be that dangerous hemorrhage occurred only in the event of sloughing tissue and in rather definite and constant time relationship. Without sloughing tissue, or before sloughing, or in connection with granulating wounds after sloughing there might be oozing but it would not increase to serious amounts. Secondary bleeding never occurred before the seventh day when death of tissue first became apparent upon observation, and hazard continued until all dead tissue had disappeared and a clean granulating wound remained. This similarity of time elements and of basic principles of technique previously noted between hospital and office procedures is evidence of common etiologic background for hemorrhage.

We wish particularly to emphasize that hemorrhage never occurred concomitantly with ineffectualness of ligatures which uniformly preceded any sloughing by days. The basic biochemical effect of sloughing tissue in producing hemorrhage is, of course, not known, but for practical purposes the reason is that the effectiveness of ligatures in the prevention of bleeding has long been spent by the time sloughing tissue begins its devastating effect.

This disunity of timing pointed the way to prevention of secondary bleeding in our office procedure and was achieved by bringing into coincidence the two time elements—that of the hemostatic protection of ligatures and that of hemorrhage initiating effects of slough. To this end an additional hemostatic ligature was easily placed in anticipation before expiration of the period of grace, viz., 7 days. Details of this do not concern us here. Suffice it to say that we have not had a single untoward instance since. In the case of a complete hemorrhoidectomy performed in the hospital, this simple solution was unfortunately impractical so that the search was turned toward details of technique which might eliminate the formation of sloughing tissue.

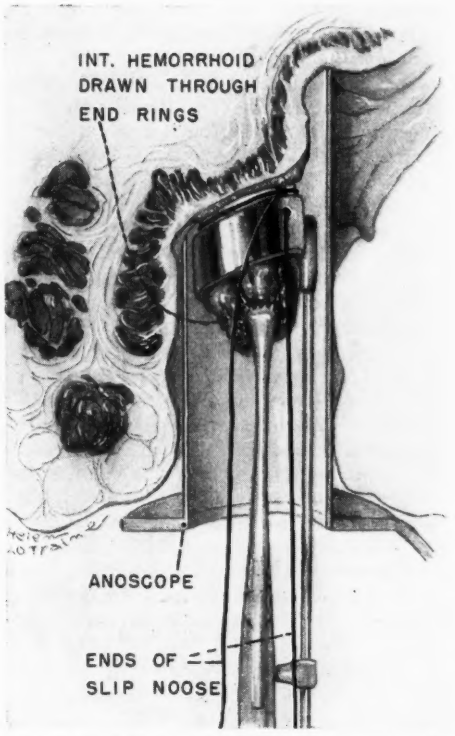

FIG. 3. Principle and method of office procedure for ligation of internal hemorrhoids.

TECHNIQUES OF OPERATION IN RELATION TO SLOUGHING

A review of the techniques in common use reveals two general and distinct patterns. One involves ligation of a pedicle with inevitable sloughing of variable, though always substantial, amounts of tissue distal to the constriction. The other consists of suturing the flat edges of mucosa to contiguous or underlying structures, which can usually be accomplished without strictured tissues which can slough.

In the ligature method basic principles are employed which were found to be responsible for hemorrhage following ligations performed at the office. It is carried out typically by dissection of the external hemorrhoidal element after which a secured ligature encircles the entire remaining pathologic tissue including the base of the internal hemorrhoid. The greater portion of the mass distal to the ligature is amputated, but

enough must be left to prevent slipping of the ligature. At best, this means death and sloughing of an appreciable amount of tissue even if the internal hemorrhoid is included in the sharp dissection. The adverse effect is compounded by concentration of a large slough within the single ligature (Fig. 1).

The alternative technique (Fig. 2) is performed by complete dissection of all hemorrhoidal tissue, amputation of the latter distal to an applied forceps, and then stitching of the mucosal flap to muscle, subcutaneous tissue, or skin. Parenthetically, such stitching as illustrated does not envision healing of the mucosa in this or other sutured position but is done solely for hemostasis. Indeed, many times we have sutured one of two similar posterior wounds in various ways for comparison with the other side left unsutured as a control. At subsequent postoperative examinations it proved impossible to differentiate the two because of failure of sutures to hold. This failure of mucosa to unite with apposed structures is really advantageous as otherwise one would fear stenosis (in the instance of longitudinal suturing as employed by some), permanent ectropion of mucosa (if sutured to skin), or particularly postoperative fistulas.

As stated, this second pattern of operation avoids, or at least significantly minimizes, sloughing and its associated hazard. This procedure has three definite advantages over the ligature method: (1) Less tissue is involved as potential slough because mattress sutures can be applied nearer to the severed edge without danger of slipping, and complete dissection eliminates the base of the internal hemorrhoid from inclusion. (2) Multiple sutures mean dispersion instead of concentration of adverse effects of constriction. (3) Interspersion of islands of normal tissue between sutures provides a collateral blood supply around and distal to the sutures with obvious favorable effect on the death of tissue. If then our basic thesis be valid—that secondary hemorrhage is due primarily to sloughing—this general pattern of operation offers substantial protection if details are understood and complied with. It is not advanced that we have provided a complete answer. Under certain circumstances it is not always possible to eliminate sloughing tissue and, in general, one should be wary of too simple explanations of complex biolgic mechanisms.

Obviously, final confirmation of the matter should include a comparison of cases following different techniques of operation for incidence of hemorrhage. This might explain also, in degree, the wide differences of reported incidence mentioned earlier. Such figures are not now available nor in early prospect. Meanwhile, speaking for ourselves, we have been impressed with our observations to the extent that we have abandoned the ligature operation and carefully plan all suturing in terms of potential sloughing.

SUMMARY

Massive hemorrhage secondary to hemorrhoidectomy is a serious emergency of undetermined incidence. A unique opportunity for observation of healing intra-anal wounds in relation to such hemorrhage is described. Evidence derived from this study implicates sloughing tissue as the predominant cause. A comparison is made between techniques of operation relevant to avoidance of sloughing which in turn suggests a substantial means of preventing the massive hemorrhage which is secondary to hemorrhoidectomy.

IMMEDIATE FROZEN SECTION DIAGNOSIS

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IMMEDIATE frozen section diagnosis in various tissues has become such a standard practice as to elicit little attention. There was a time when it was considered an event. Hours were spent in preparation; messengers stood by to hurry the specimen along its way; and the telephone was cleared for the ensuing report. Despite the replacement of such a demonstration by ordinary adjustments to the routine daily work in the laboratory, it is wise to evaluate its present status in the analysis of disease.

The purpose of the method is to render to the surgeon a report on any questionable piece of tissue as quickly as possible. The delay associated with the preparation of paraffin sections makes permanent methods unavailable to immediate diagnosis. However, with freezing, time may be reduced to minutes. With the report at hand, the surgeon may then decide on the type and the scope of the operation. It is advisable to emphasize that sound clinical judgment is not replaced, but rather augmented, by this procedure. While some surgeons prefer to depend on gross interpretation only, others, though quite certain of their conclusions on direct study, wish verification from a pathologist in whom their confidence has been established.

To be of greatest value to the patient, the surgeon and the pathologist must be cognizant of the mutual responsibility assumed by both, as well as of the limitations and sources of error inherent in any procedure of this nature. The surgeon should obtain an adequate and representative segment of the tissue in question. This procedure is his responsibility and its importance cannot be overemphasized for it represents a possible source of error. Moreover, the origin of the tissue must be clearly stated either verbally or in writing, i.e., on the label. At this point it may be mentioned that the use of a third party, be it a nurse, intern, or an attendant, to convey the tissue or any relevant information to the pathologist should be avoided as much as possible, for herein lies another potential source of error. The third one is in the interpretation of the section. The pathologist must have an adequate and satisfactory background in the principles of pathology as well as experience. The more material he has seen, the more frequent his commitments, and the greater the number of checks against permanent sections, the more he may contribute to the diagnosis in question. The limitations and errors in diagnosis as they arise in various tissues will be discussed in detail later.

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The degree of usefulness of, and proficiency in, frozen section technique hinges upon its widespread application by the pathologist. The more the procedure is applied to all tissues and organs, the greater the benefit from its success. Certainly, no one can foretell its specific value in a definite instance without at least trying the method. It may be mentioned that many physicians question the value of the use of frozen sections. In a similar fashion, many pathologists are averse to the use of the technique, or consider it a chore. If a pathologist believes in the procedure he will use and recommend it to the clinician. If he is opposed to it, or thinks it a burden, he will imply his beliefs to the surgeons.

It is our wish to recommend that permanent sections of surgical specimens not be replaced thus. We prefer this method for surgical and autopsy tissues, and frozen section for immediate diagnosis in the operating room or for confirming a gross conclusion at the autopsy table. Because of our laboratory arrangements, one microtome is kept in the operating room, a second with accessories in the tissue room, and a third in the autopsy room. In the two latter locations, we are prepared to satisfy natural curiosity and make a frozen section of autopsy tissues as well as surgical specimens for which no request has been made. As an autopsy is being performed, if a question arises as to whether a nodule in the pancreas is a primary or secondary tumor, or even a neoplasm, an immediate frozen section is made. This action may avoid a great deal of useless philosophic discussion. The residents are encouraged to make such frozen sections a part of the routine day. Thus, they lose fear of both the technique and the interpretation. The amount of time lost is minimal when compared to the

energy and time dissipated through pointless argument.

On the subject of technique, it is imperative for the readers to understand that these are our own ideas and apply to the hospital in question. Certain phases may not of necessity be applicable in other institutions. One of us (M.C.W.) has had the opportunity to perform frozen sections in quite a number of hospitals with different methods and equipment. From this experience, we have devised the technique now used.

If possible and provided the laboratories are some distance from the operating room, it is better to freeze and stain the sections in a room on the same floor. In our hospital such a room is provided and used exclusively for this purpose. A well oiled and tended microtome is at hand as well as several heavy sharp knives. Carbon dioxide tanks are replaced before they are completely empty so as not to exhaust the supply at a critical time. Since we prefer unfixed tissue, the specimen is not boiled in formalin. Thus distortion is avoided and minutes are saved. Two staining methods are used on all sections. On all specimens a gross conclusion is first reached. After selecting the block of tissue, it is immediately frozen with short numerous turns of the carbon dioxide tank. This procedure is economical and also prevents too dense freezing. Sections are cut at 10 microns, and the tissues are transferred to Petri dishes containing cool tap water. The working desk surface is black. The sections are teased onto albumin coated glass slides. The first is stained with a polychrome dye (alcohol-carbol-thionine) mounted in glycerine, covered with a thin cover slip, and is immediately available for microscopic study. The other section is dried quickly and then dehydrated with drops of absolute ethyl alcohol. When this has been done, it is stained by a rapid hematoxylin and eosin technique, mounted in a permanent medium, covered, and is ready for interpretation. It is important that this slide later be filed with the permanent sections for comparison or verification. Some of these preparations are most satisfactory and may, from time to time, be better than inadequately fixed or stained permanent sections. Similarly, it is always advisable to process by the paraffin method for permanent file that segment of tissue used for the frozen section. By several computations it is estimated that a thionine stained section is prepared in 2 minutes. To save time while the senior pathologist is interpreting the thionine preparation, one of the residents prepares the hematoxylin and eosin slide which takes 5 minutes.

We believe that the pathologist or the residents should do all the technical work. A well stained and prepared slide is a *sine qua non* to accuracy in microscopic interpretation. Because of its importance, it should not be left in the hands of a technician. It has been our observation that diseased tissue, especially if containing a malignant tumor, cuts in such a fashion as to give an indication of the diagnosis which would not be recognized by a technician.

Because the residents receive careful instructions, they are allowed to read all slides independently, and a general discussion is carried on following the report which is made in the simplest fashion: a direct statement to the operator through the door of the operating room. If there is disagreement, more sections may be cut or more tissue may be analyzed. Contrary to others who have expressed themselves on this subject, it is our policy to give the diagnosis in full—an astrocytoma rather than a glioma, a lymphosarcoma rather than a malignant lymphoma, a metastatic carcinoma in bone probably from the kidney, and so forth. Furthermore, we prefer not to have a preconceived idea of the case in question. After a diagnosis has been established, the clinical data are sought or obtained at the time of reporting to the surgeon. In most instances, it is not difficult to be definite in the conclusions. In other instances, clinical data are beneficial in arriving at an interpretation. In a very few cases only, is a definitive diagnosis not possible.

ACCURACY IN DIAGNOSIS

Of most importance both to the surgeon and the pathologist is the degree of accuracy obtained in diagnosis. For this section of our discussion it is necessary to rely upon an unpublished study which one of us (M.C.W.) undertook with the late P. J. Clark while working in the laboratory of Shields Warren in Boston. Approximately 3,500 frozen sections performed during a 10 year period prior to January 1942 were analyzed and compared with the interpretations made in the permanent sections. As a base line, it was assumed that the conclusions on the permanent sections were correct. In addition to these figures, we have kept fairly

accurate data on the sections performed in this and in other hospitals. It is realized that the highest degree of accuracy in interpretation is obtained in the tissue or organ for which the diagnostic procedure is used most frequently.

Breast. The ideal accuracy would be 100 per cent; in the study made, it was 98.5 per cent. It must be mentioned that specific conclusions were always given and hedging was at a minimum. In only scattered instances was it recommended that the frozen section was not satisfactory for diagnosis and that there be a delay of 24 hours until the permanent sections were available. Although the interpretation was based on the presence of a carcinoma, still an attempt was made to catalogue the neoplasm as to degree of anaplasia, extent, and such other information as would prove helpful to the surgeon.

Three errors were recorded because of failure to obtain a representative sample for study. While it is true that the pathologist sections the entire specimen submitted, the marking of suspicious areas by the surgeon with silk sutures is of value, especially if the tissue submitted is bulky.

The carcinomas present no problem, except possibly the so-called comedocarcinomas in which, usually in the frozen section preparation, a layer of malignant cells lining cystic structures may be the only clue to the diagnosis and may be easily overlooked. Sarcomas may present more difficulty; however, the bulkiness and consistency of the tumor on inspection will aid in the conclusion.

Among the nonmalignant lesions, a florid sclerosing adenosis may be troublesome. Here, the consistency of the gross lesion and a good hematoxylin and eosin stained section will help in arriving at a definitive diagnosis. The papillomas are usually found by the surgeon. Inflammation, hematomas, and fat necrosis are easily recognized in the gross specimen and on microscopic study.

Brain and spinal cord. Because there is a very active neurosurgical service in this hospital, it has been necessary to develop accuracy in frozen section diagnosis of brain lesions. The neurosurgeon usually can determine the various types of intracranial lesions macroscopically. However, he may prefer confirmation by frozen section. Also, it may be possible to learn if the excision is beyond the tumor in the case of gliomas. We have been accurate in the diagnosis of gliomas except for a tendency to underdiagnose the degree of anaplasia, i.e., astrocytoma instead of glioblastoma multiforme. The medulloblastomas present a specific histologic picture. Meningiomas and neurinomas offer no problem except for the rare malignant variant of the former.

Metastases from a primary tumor elsewhere usually are correctly interpreted. There is difficulty when an attempt is made to determine the original site. The surgeon must be aware of this limitation of the procedure. However, it is wise to recall the predilection of rectal carcinomas to spread to the posterior fossa via the vertebral veins. Bronchogenic carcinomas, likewise, metastasize to the brain in about a third of the cases; the oat-cell form is usually obvious microscopically.

Much of what applies to intracranial lesions may also be used for changes in the spinal cord and surrounding membranes.

From the technical point of view, it may be said that the thionine method offers more than the hematoxylin and eosin technique in the diagnosis of brain and spinal cord lesions.

Bone. The use of the immediate frozen section for diagnosis in bone diseases has one hazardous feature, that is, the technical difficulties. If there are no spicules and if the osteoid is not too dense, a preparation is possible. Malignant change is often readily interpreted. The diagnosis must be correct, however, to avert an unnecessary mutilating amputation. In case of doubt, wisdom counsels delay. Nevertheless, certain neoplasms are easily catalogued. Perhaps the procedure is of greatest value in recognizing metastatic tumor and nonneoplastic entities such as tuberculosis, syphilis, lipid dystrophy, and such. Giant cell tumors are fairly easy to recognize, the malignant variant more difficult. In the series of 3,500 frozen sections referred to previously, there was a satisfactory degree of accuracy in diagnosis of bone lesions. Clinical data and roentgenograms are very contributory to the diagnosis.

Lungs. The procedure is used to confirm the diagnosis of lesions in the lung, inflammatory or neoplastic, so as to ascertain the type and extent of operation. Chronic granulomas, hamartomas, and other nonmalignant tumors are readily diagnosed. Primary carcinomas, in general, offer no problem. Bronchiolar carcinomas and bronchial adenomas may be more difficult.

Differentiation between oat-cell carcinomas and malignant lymphomas is not easy, but malignancy can usually be determined. Mesotheliomas may be interpreted less accurately.

Kidneys. Subcapsular neoplasms, as well as inflammatory conditions clinically evident or unsuspected, may be diagnosed by the frozen section method. Malignant lymphomas are not a problem. The procedure is recommended especially in those cases in which the gross appearance of the kidney at the time of operation does not coincide with the preoperative impression.

Ureters. Papillomas and carcinomas can be seen macroscopically and then be confirmed by frozen section. The granulomas can be identified microscopically.

Urinary bladder. The differentiation between transitional cell papillomas and the malignant variants is a problem unless stromal invasion is demonstrable. Carcinomas in situ are difficult while the inflammatory diseases are easily diagnosed.

Prostate. Immediate frozen section diagnosis is used in perineal biopsies of the gland prior to radical prostatectomy if carcinoma is found. We have not been afforded an opportunity to study the prostate under these conditions.

Testis. Malignant tumors can be identified but classification as to type may prove a problem. In the selection of a suitable block for sectioning it must be borne in mind that a small nidus of teratocarcinoma may be present and easily overlooked. A malignant lymphoma may be confused with chronic inflammatory conditions of the testis; tuberculomas, however, can be diagnosed.

Ovaries. The inflammatory processes, endometriosis, fibromas, and fibroleiomyomas offer no difficulty. Dysgerminomas, thecomas, and granulosa cell tumors are all interpretable. Much difficulty is experienced in distinguishing malignant change in certain cystadenomas as well as the malignant variants of granulosa cell tumors. This is due for the most part to limitations inherent in the procedure itself and must be recognized by the surgeon as such. It is in these instances that a good hematoxylin and eosin preparation is valuable; even so, because of fixation shrinkage, distortion may make interpretation difficult.

Oviduct. Requests for frozen sections of the oviducts are uncommon. However, malignant lesions and inflammatory conditions can be diagnosed.

Uterus. Much variation of opinion exists concerning the use of immediate frozen section in the diagnosis of uterine curettements. Its value rests in the fact that if carcinoma is proved at the time of operation, the patient may be saved time and money and be spared a second anesthetic. The success of the procedure depends on the ability and experience of the interpreter and the amount of representative tissue available for examination. The hematoxylin and eosin stain offers the most help in endometrial carcinomas which means that the section must be well prepared and well stained. Differentiation between atypical hyperplasia and a low grade adenocarcinoma may not always be possible. Sarcomas as distinguished from myomas do not necessarily present a problem. Fairly extensive cervical lesions may be easily sectioned for study and diagnosis. Dysplasias and carcinomas in situ are not easy to differentiate. Polyps, physiologic hyperplasia, atrophy, and inflammatory states are usually easily determined.

Parathyroid and thyroid glands. In only a few instances has it been our problem to decide on parathyroid lesions and these have been associated with adenomas or hyperplasia. They are most difficult to diagnose and require some experience. On the other hand, requests for help on lesions of the thyroid are common. The adenomatous goiter, the strumas, and the adenomas rarely present difficulty. The malignant variants of the adenomas or the outright carcinomas offer more of a challenge. Because of the size of the tissue submitted, the difficulty lies in the choice of a representative area for section and study. Invasion of the capsule, the veins, or the lymphatics, alone or in combination if definite, will prove adequate, if there is associated morphologic alteration of the gland. The presence of thyroid tissue, even if obviously normal, in a lymph node is interpreted as metastasis.

Liver. Inflammatory, as well as secondary, lesions of the liver from systemic diseases are difficult to classify. Secondary tumors are identified as such, although the primary source may not be evident. A hepatoma superimposed on portal cirrhosis may be a problem since the tumor cells are usually well differentiated. Adenocarcinomas of the intrahepatic portions

of the biliary system are readily recognized if the site of origin is noted grossly. Granulomas of the liver do not present a problem.

Gallbladder and biliary passages. Papillomas and carcinomas of the gallbladder are recognized grossly and are accurately diagnosed upon microscopic study. Heterotopic tissues simulating malignant neoplasms can be identified as such. Adenocarcinomas arising from the biliary tree, and especially if situated at or about the ampulla of Vater, may be extremely difficult to differentiate from normal glands native to the area. Multiple blocks should be studied and a meticulous search for perineural lymphatic invasion should be made.

Spleen. Requests for frozen sections from the spleen are uncommon. However, primary and metastatic tumors, though rare, can be diagnosed grossly and verified upon microscopic examination. Hyperplasia of the spleen is difficult to ascertain by this procedure.

Technically speaking, the spleen, like lymph nodes, shreds easily and is difficult to section. This difficulty may be obviated by cutting the tissue at 20 microns.

Pancreas. Adenocarcinomas of the pancreas are well differentiated as a rule and are extremely difficult to distinguish from normal pancreatic acini. Perineural lymphatic invasion is conclusive evidence of malignancy. Inflammatory conditions are not a problem.

Adrenal gland. Tuberculosis, metastatic tumors, and adenomas are easily identified by this procedure. The primary carcinomas are rare and are usually suspected on gross examination. Pheochromocytomas are not a problem.

Pituitary gland. We have had occasion to use this technique on tumors of the pituitary gland. The adenomas, particularly the chromophobe type, and the craniopharyngiomas have definite histologic patterns. The malignant lymphomas may be more difficult to distinguish.

Gastroenteric system. Most of the lesions, especially the malignant ones, as seen in the gastroenteric tract are rather easily diagnosed grossly. Microscopic interpretations of immediate frozen sections present a minor problem. Those in the tongue and lip are indicated to determine the degree of virulence of the neoplasm and also to find out whether or not the surgical borders of excision lie beyond the tumor. Elsewhere in the oral cavity, the same statement applies. Problems arise in the salivary glands, especially in the mixed tumors in which malignant transformation is suspected. However, the degree of accuracy may be fairly high.

Anaplasia and the extent of tumor, especially the depth, are the two major uses for immediate frozen section in the esophagus.

Perhaps the greatest challenge in diagnosis of lesions of the stomach lies in the chronic ulcer in which there is some suspicion of carcinomatous change. It is wise to make several sections at various sites, even then the problem is not easily solved. Depth of penetration of a diffuse carcinoma is also a requirement of frozen section reports, if gastrectomy is to be advised. Hodgkin's disease, lymphosarcomas, and leiomyosarcomas are all diagnosed with experience. An incipient carcinoma in a papilloma presents difficulties. It is wise to study the pedicle where invasion is most likely to show. Nonmalignant encapsulated tumors present difficulty only in classification. Metastasizing and invading tumors of the stomach may be confirmed by microscopic study, though this may not be easy to do, particularly if the primary site is in the pancreas, for example. Inflammatory entities present less of a problem.

Much of what has been said applies to the appendix and the small and the large intestines. Here, in addition to the tumors already mentioned, one must be certain to rule out the various inflammations. Diagnosis of carcinoids must be made with this technique. Immediate study of regional lymph nodes may likewise be requested.

Skin. The procedure is used primarily for diagnosis and to determine whether the borders of excision are adequate if a tumor is malignant. The diagnosis of squamous and basal cell carcinomas is fairly easy. The active junctional nevus as well as the juvenile melanoma is a problem, particularly if the age of the patient is not known. Malignant melanomas showing dermal invasion are recognized by using this procedure, though at times difficulty may be encountered. Inflammatory conditions of the skin are a problem only insofar as classification is concerned.

Connective tissues. In the diagnosis of connective tissue neoplasms the purpose of the procedure is to define the scope of the operation. Malignant tumors are readily identified microscopically, but their classification may prove troublesome. Well differentiated liposarcomas and malignant

schwannomas can be recognized. Difficulty arises in distinguishing rhabdomyosarcomas, neurofibrosarcomas, fibrosarcomas, and the malignant variant of dermatofibromas.

DISCUSSION

Immediate frozen section diagnosis as an aid to the surgeon has two principal uses: (1) to ascertain the nature of the lesion in the organ(s) or tissue(s) immediately, and (2) to determine whether the surgical borders of excision are beyond a malignant tumor, by that means insuring the complete extirpation of the neoplasm.

The surgeon must know when to ask for a frozen section diagnosis and what to expect from the report in a given situation. He must, therefore, be aware of the limitations and possible sources of error in the procedure. As mentioned, these are failure to obtain an adequate and representative sample of the tissue in question, and second, errors in interpretation.

Errors in interpretation can be reduced to a minimum if the pathologist is experienced and proficient in the use of the procedure. To attain both demands constant application of the technique to any and all tissues, whether in the operating room, the autopsy room, or in the laboratory on surgical specimens. It is only in so doing that he gains confidence in interpreting slides and in preparing good stained sections. The diagnostic accuracy of an examiner depends largely on the quality of the tissue sections under study.

For those who doubt the value of this procedure, we have to ask the question: "What benefits accrue to the patient if, at the time of the operation, the nature and extent of the disease is known to the surgeon?" If the disease is malignant, total extirpation of the tumor and surrounding tissues may be done, thereby saving the patient a second operation with its attendant risks and worries, time, and money. If the lesion is nonmalignant or inoperable, there will be no needless sacrifice of tissue or prolongation of operating time. If we can help the surgeon do this much good for the patient at the time of operation, we believe that the procedure is justified and hence of value.

SUMMARY AND CONCLUSIONS

1. The value of immediate frozen section diagnosis to the surgeon and indirectly to the patient is discussed.

2. The procedure employed in this hospital is outlined. Proficiency in preparing and staining of sections is essential if accuracy in interpretation is to be attained.

3. The limitations and possible sources of error are listed and discussed in general and are then described in detail for the various tissues and organs.

DETECTION AND LOCALIZATION OF PRECLINICAL CARCINOMA OF THE CERVIX BY CONTACT SMEARS

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IT IS AN ESTABLISHED FACT that the value of cytologic smears lies in the detection of preclinical carcinoma of the cervix in women who present either a normal or benign appearing cervix. Any change in the present simple methods of obtaining smears would be justified only if the new procedure would offer definite technical and economical advantages over the conventional techniques. The contact smear may offer such possibilities.

The usual vaginal pool smear is admitted to be productive of smears containing "dead and decaying cells, bacteria, and much detritus" (2) which makes the screening of these slides difficult because of the presence of cellular elements and debris not essential to the detection of cancer cells. In a sense, this extraneous material dilutes the number of malignant cells so that it is necessary to laboriously screen the length and breadth of the standard 1 by 3 inch slide for fear of overlooking a single or group of malignant cells which might lie only in one small section of the smear.

The development of the superficial or surface biopsy-like smear obtained directly from the cervix as a cytology specimen was a natural and rewarding improvement. This type of smear contains a greater concentration of well preserved malignant cells which lend themselves to screening detection in much less time than is required for a vaginal pool specimen. This feature of the cervical smear is responsible for the comment made by some cytologist that the screening of a smear seldom required more than a few minutes. It is true that in a large number of correctly obtained smears a great many malignant cells may be present and permit detection within a few minutes of screening. It should be understood, however, that in cases of a reported negative result, random fields may have been screened without the detection of cancer cells. This rapid screening has as its basis the opinion of some cytologists that certain features of the benign epithelial cells suggest the possibility of the presence of malignant cells in the smear. Apparently it is believed by some that in clean smears lacking this "cellular indicator" a negative report may be given after a few minutes of random field screening. To depend upon a large number of malignant cells invariably being present, and abnormal features of benign epithelial cells to serve as a possible warning of their presence, is not reliable enough to preclude a thorough search of each smear, field by field, to make certain that malignant cells may not be present in an unscreened portion of the smear.

The disadvantage of the vaginal, cervical, and endocervical smears is that very often they are poorly taken and are unsatisfactory for interpretation. As simple as the preparation of a smear appears, all too frequently they are made either too thin or too thick, or are allowed to dry out before fixation. Furthermore, in the transfer of material to the slide, mechanical folding, clumping, and piling up of cells occur frequently, thus obscuring the morphology of many of the cells. A more important and ever threatening possibility is that the smears may not represent the epithelium from the squamocolumnar junction, the site of more than 90 per cent of the cervical cancers. There is no landmark to guide one to this important anatomic site, and I fear that in many instances this area is not represented in the smear. It is not commonly appreciated that when the cervix is visualized with a speculum, extension of the speculum blades everts the cervical lips and what one actually sees is the exposed endocervix. Smears taken from the normal red appearing endocervix which is often mistaken for cervicitis may be far removed from the junctional zone, and completely miss a malignant lesion occurring at the junctional zone or out on the face of the cervix. These factors contribute to the increased cost of cytologic investigations and are responsible for delay and a great deal of anxiety in apprehensive patients who are required to return for repeat smears.

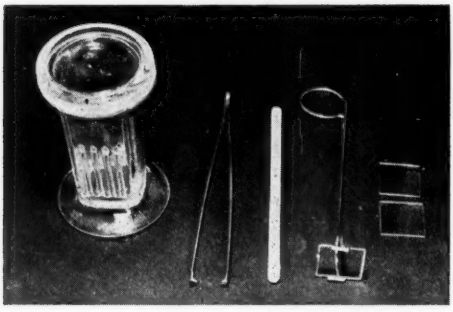


FIG. 1. Simple set up for contact smears: Coplin jar containing equal parts of 95 per cent alcohol and ether, pick up forceps, narrow stick, slide carrier, special 1 by 0.875 inch slides.

CONTACT CYTOLOGY SMEARS

The use of contact smears for cytologic studies is not new. It has found its greatest use in the fields of dermatology and hematology. Those of us who used the method on known gross malignant operative specimens in our earlier years of cytologic training were struck by the sharp, clear-cut, and undistorted structure of the malignant cells so transferred. For a number of years I have been interested in finding a method of obtaining transfer or contact smears from the cervix. The reported method, I believe, is most satisfactory and practical. The technique and advantages as pointed out in this brief preliminary report may solve some of the technical and economical disadvantages of the present conventional procedures.

The most important prospect of the contact smear is the possibility of localizing a preclinical microscopic focus of cervical cancer. It is generally appreciated by cytologist and gynecologist that an early focus of preclinical cervical cancer may be but a few millimeters in size at the time the patient first presents herself for examination. It is not impractical to think that a transfer image of this small lesion onto a contact smear is beyond reasonable expectation. Personal experience leads me to believe that it is possible.

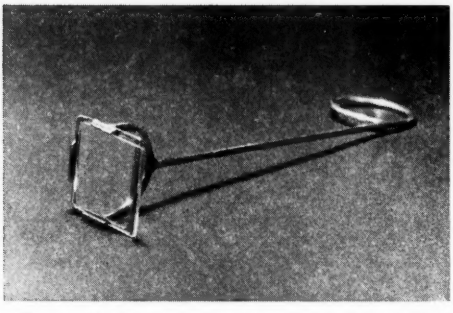


FIG. 2. Detailed view of slide carrier with partially inserted slide.

TECHNIQUE OF OBTAINING CONTACT CERVICAL SMEARS

The complete face of the cervix can be covered by a slide 1 by 0.875 inch in diameter. The slide carrier, which accommodates this small slide on its leading face, is attached to a long handle, which is slightly curved in order to give an unobstructed view of the application of the slide to the surface of the cervix (Figs. 1 and 2). The slide has a frosted margin on one side only, which serves as patient identification as well as orientation of the smear. The slide is always placed in the carrier with the frosted margin down and facing the operator (Fig. 3). In this position the center of the slide will represent the cervical os; the area below it and adjacent to the frosted margin, the posterior lip of the cervix; the opposite side of the slide above the cervical os area, the anterior lip. The left side of the smear, as it is viewed by the screener, will be a mirror image of the right side of the cervix, and the right side of the slide, the left side of the cervix.

The cervix is exposed with either a vaginal or a small weighted speculum. When a Graves or similar type vaginal speculum is used, introduction of the slide carrier is facilitated by extending the blades of the speculum to its maximum capacity (Fig. 4). This is easily done by enlisting the patient's co-operation with an explanation of the type of pressure which will be applied, slowly and gently. Patients undergoing such a procedure are invariably co-operative and anxious that a satisfactory specimen be obtained. The cervix and vagina are gently cleansed of excessive vaginal secretions with a bulky cotton applicator. Gentleness is important as it is possible to knock off a small focus of surface cancer by a too vigorous cleansing of the cervix. The carrier is introduced into one of the oblique diameters of the vaginal speculum. On entering the vaginal cavity, the carrier is rotated to its normal position with the frosted end of the slide down. The speculum is then relaxed

slightly allowing the cervix to resume its normal shape and approximation of the cervical lips. The lips are not permitted to approximate completely, as it is desirable to have a small portion of the endocervix exposed for the contact smear. The cervix is viewed through the glass slide in a window-like fashion, and the cervical os is centered on the slide. The slide is then firmly but gently pressed against the cervix and rotated to either side about 3 degrees. Too much pressure or excessive rotation of the slide will produce smears that are too thick with clumping, crowding, and distortion of the cells, and should therefore, be avoided. The carrier is then withdrawn; the slide is removed and put smear side up in a Petri dish or on edge in a Coplin jar with equal parts of 95 per cent alcohol and ether.

In those cases in which there is marked hypertrophy of the cervix or distortion and irregularity due to an old laceration of the cervix, contact smears of each lip are made separately.

In addition to the cervical contact smear, and in order to cover the possibility of cancer proximal to the junctional zone as well as the endocervix itself, an endocervical smear is made. A suitable and efficient method for obtaining endocervical smears involves the use of a narrow wooden stick (0.25 by 5.5 in.) which can be inserted into the average parous cervical os and canal. The stick is rotated 360 degrees and the smear is transferred to a 1 by 0.875 inch slide. Mucus and cells cling readily to wood and can be easily transferred onto a slide without drying out, as frequently happens when a cotton applicator is used. These two smears, the contact and endocervical, assure survey of both areas, distal and proximal to the squamocolumnar junction as well as the endocervix.

ADVANTAGES OF THE CONTACT CERVICAL SMEARS

It is practically impossible to miss the important anatomic point of interest, the squamocolumnar junction. There is an accurate transfer of the cervical epithelium—a cellular photograph, so to speak—onto the slide. When properly taken, all of the smears are of the desirable 1 cell thickness without distortion, overlapping, or crowding, and without superfluous cells. The central portion of the smear representing the cervical os area is typically thin and scanty. The periphery of the slide is denser in appearance because of the richer source of cells in the anterior, posterior, and lateral surfaces of the cervix.

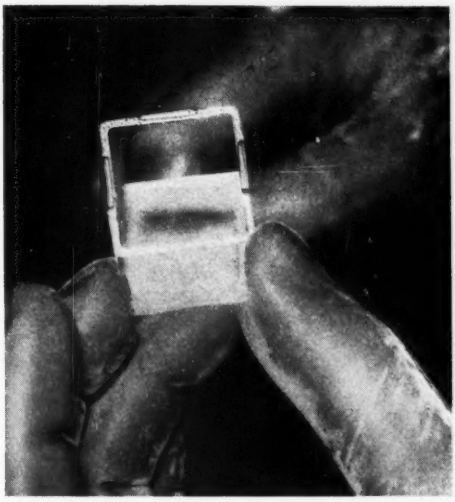


FIG. 3. Loading slide carrier with special 1 by 0.875 inch slide with frosted edge down, facing operator.

PROCESSING CONTACT SMEARS

These small slides are processed in the same manner as their conventional counterpart, 1 by 3 inch slides. Staining follows the recommendations of Papanicolaou. The standard slide-holding stain rack as illustrated in Figure 5 was altered to accommodate the 1 by 0.875 inch slide. Small narrow icebox food containers serve as convenient and satisfactory staining trays. These small trays, with just enough room for the solutions and staining rack, conserve and economize on solutions and stains and reduce clutter and space requirements.

Mounting the slide with a cover slip can be carried out by use of a special jig to hold it during the process, but we have found it is just as easy to mount these small slides without the jig. To evaluate the ease of staining and mounting these 1 by 0.875 inch slides, we experimented by using an untrained office assistant without any type of laboratory experience. She was able to follow the procedure after a brief session of direction without the use of the jig for mounting.

SMEAR SCREENING

A special jig is necessary to hold the slide in the mechanical stage for screening. It is a small metal slide 1 by 3 inches in diameter with a window in the center that will accept and support the slide.

FIG. 4. Cervix viewed through the slide applied against the cervix with the cervical os centered on the slide. A Graves speculum is usually used. The weighted speculum and tenaculum used only for photographic purposes.

Since the smears are uniformly thin, screening is rapidly carried out within a matter of a few minutes. Because of the cohesive deficiency of malignant cells, smears taken from a patient with preclinical carcinoma contain a great number of pre-exfoliated malignant cells in a state of good preservation which permits almost instantaneous detection. Under the low scanning objective, a few turns of the mechanical stage knob will enable the viewing of the entire smear, and even under this low power, nests of hyperchromatic cells can be easily spotted and then studied under higher magnification. This concentration of malignant cells must actually be seen to be appreciated.

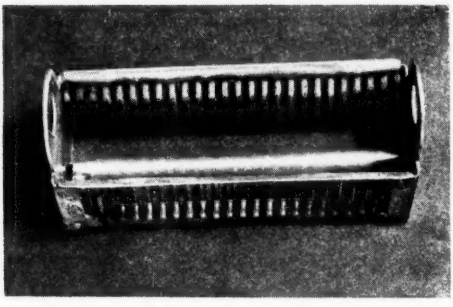


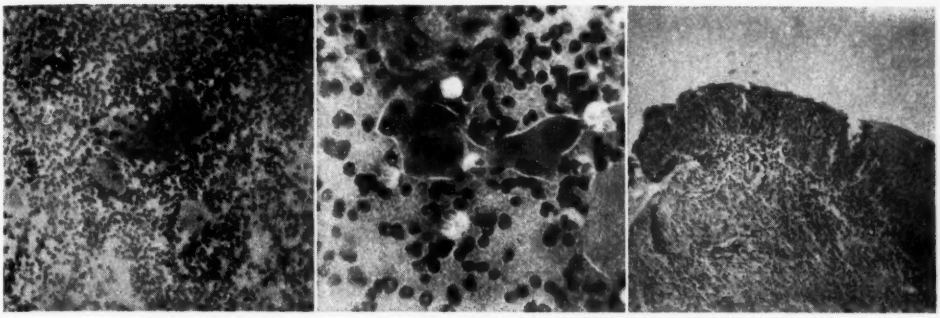
FIG. 5. Standard stain-rack altered to accommodate a 1 by 0.875 inch slide.

When conventional and contact smears are taken simultaneously, the rapidity of detection of malignant cells in the contact smear over the other is most striking. The screening of a contact smear does not produce the maddening boredom and occular fatigue experienced in the examination of the conventional smear which is so packed with cells and debris that it requires from 15 to 30 minutes to screen. There is a sensation of impending completion in the screening of a contact smear that is never experienced with the standard smear, and this is conducive to accuracy and thoroughness. It has been conservatively estimated by McLaren that "occular fatigue limits microscopy to 3 to 4 hours" of actual working time, "or about 16 to 18 slides a day" when using the conventional smears. If a technician usually screens 4,000 to 5,000 smears a year, he should be able to screen 10,000 to 12,000 contact smears a year.

Roughly in 99 per cent of the smears screened the result will be negative. This finding is therefore a source of concern, posing a problem of accuracy, perhaps not in some cytologic laboratories which are located in large medical teaching centers that are staffed by an adequate number of cytotechnicians of long experience who are supervised by expert full-time cytologists, but in those areas without these advantages. The contact smear makes it unnecessary for a busy, harassed cytopathologist to content himself with random field observations in spot checking negative reports. He can actually check the entire smear in less time than he usually spends for an incomplete check of the standard smear. Statistics on false negative reports are not accurate unless the smears are correlated with a biopsy taken at the same time or unless all of the smears reported negative are carefully and completely reviewed by the cytologist. In effect, then, if the smear is easily screened and the checking of all negative results is within the realm of possibility, the use of contact smears should result in a decrease in false negative reports and a more realistic figure for false negative statistics.

LOCALIZATION OF A PRECLINICAL FOCUS OF CERVICAL CANCER

Experience with the contact smear has indicated that it may be possible to pinpoint a microscopic focus of preclinical cancer. When



a b c

FIG. 6. J. T., age 35, with benign appearing cervicitis. Contact smear suggested anterior lip lesion. a, Group of malignant cells. b, High power view showing interesting mitotic figures. c, Tissue section showing carcinoma in situ.

the lesion is small and confined to one of the lips or angles of the cervix, the concentration of malignant cells in a corresponding area on the transfer smear suggests its possible location on the cervix. If the lesion is multicentric, this may likewise be represented in the smear. When the concentration is prominent in the center of the smear (external cervical os area) one should suspect extension upward into the endocervical canal or endometrial carcinoma. The possibility of contamination of a specific area of the slide by malignant cells originating from another part of the cervix is occasionally to be expected.

In the presence of a smooth, clean, or innocent looking cervix, a smear-localized lesion eliminates the hit or miss nature of random biopsies and permits the clinician to go directly to the suspicious area of the cervix for a biopsy. It also directs the pathologist to the suspected area of a "coned cervical specimen" for a more detailed sectioning of that area for histologic study. It is desirable to take a biopsy specimen from the site of a smear-localized lesion and then continue the biopsy in the four cervical quadrants and any other Schiller positive area. These specimens are put into separate bottles and labelled as to location, and a notation is made as to the smear location of the lesion.

Adenocarcinoma of the endometrium has not been encountered thus far in the contact smear program. In adenocarcinoma of the endometrium, it is believed that if exfoliated cells were present in the endocervix, one should expect to detect them in the central portion of the smear.

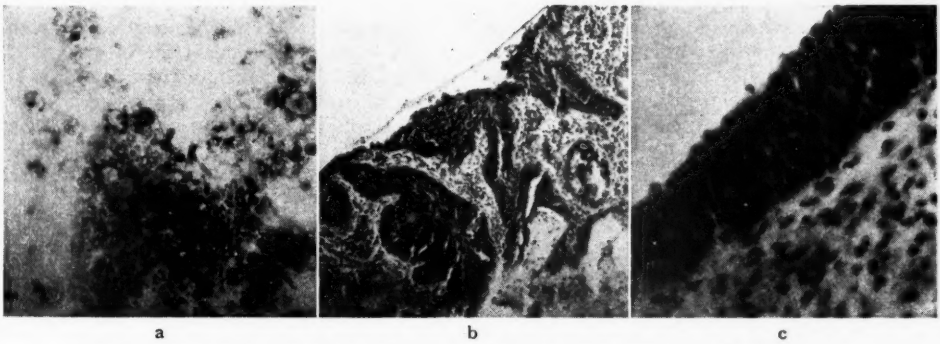


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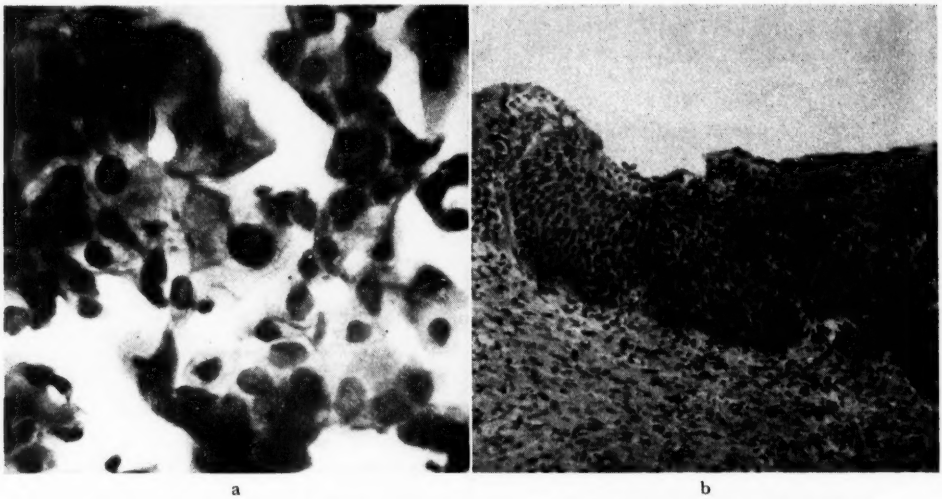
FIG. 7. Patient V. D., age 32, 4 months pregnant. Contact smear suggested preclinical carcinoma of posterior lip and right lateral aspect of the cervix. a, Group of malignant cells in posterior cervical lip area of contact smear. b, Tissue section showing carcinoma in situ and showing gland involvement. One area suggestive of early invasion. c, Tissue section showing carcinoma in situ.



a b

FIG. 8. Patient J. B., age 33. Cervical stump smooth and without clinical disease. Routine vaginal cytology positive for malignant cells. Contact smear suggested lesion confined to anterior lip of cervix. a, Group of malignant cells showing crisp sharp one cell thick smear when contact is gentle. b, Biopsy specimen showing carcinoma in situ. Cervicectomy specimen failed to show residue of lesion which evidently was removed completely with biopsy forceps.

These cells should be less degenerated and more easily detectable than the endometrial cells shed into the vaginal pool. It may be of advantage when taking a contact smear to produce a to and fro pumping action against the cervical os in the hope of securing endometrial cells lying low in the endocervix.

ECONOMICAL ADVANTAGES OF THE CONTACT SMEAR

Frequent objections to the routine use of vaginal smears have been the cost to the patient, as well as the lack of time and scarcity of cytotechnicians in busy pathologic laboratories far removed from medical centers. The cost of processing and screening contact smears should be effectively reduced by virtue of the marked increase in productivity of the cytotechnician and the volume decrease in fixatives, costly alcohols, and stains. All of this should reflect a considerable saving to the laboratory and, more important, to the patient.

Storage space, always a premium in any laboratory, should accommodate 3 contact smears in the space required for 1 standard slide. A suitable slide holder is a special cardboard pocket-like arrangement which is simply made by stapling pockets onto an ordinary filing card as done in the Papanicolaou laboratory.

DISADVANTAGES OF THE CONTACT SMEAR

The contact smear requires physician participation, visualization of the cervix, and the handling of a small slide. This fact eliminates it as a method for mass screening by the use of nonmedical personnel. This latter disadvantage is actually an advantage. Patient-doctor contact is important and desirable. Although cancer of the cervix is the most frequent site of gynecologic cancer, the labia, vagina, uterus, and ovaries are not of insignificant importance in cancer detection. One European monograph on cytology intimates that American physicians no longer examine patients for cervical cancer, but utilize smears. Of course, this comment is ridiculous, but it is significant.

The encouragement of routine smears by every physician in institutions and private practice could come very near to accomplishing population screening if a simple, rapid, and inexpensive method of cytologic study were available. The contact smear may meet this requirement. Whoever made the statement that every doctor's office should be a cancer detection

center gave us the best blueprint for tackling this urgent public health problem of cancer control.

This preliminary report, without statistical data, was prompted by the reaction of colleagues with whom I discussed the procedure and some of whom have furnished clinical material. It is quite obvious that unless a large source of positive material were available for data accumulation, many years would be required to gather valid evidence for the evaluation of the contact smear. This observation is borne out by the fact that although investigations were started in 1953, there is still insufficient statistical data for publication. I have, however, had sufficient experience with the method to know that it is worthy of further investigation. It is hoped that others having a large source of tumor material will interest themselves in a clinical evaluation of cervical contact smears as related to the localization of preclinical cancer of the cervix as well as to the technical and economical advantages.

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A COLLAPSIBLE TUB FOR IMMERSION COOLING ON THE OPERATING TABLE

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SURFACE COOLING provides a simple and practical method of inducing hypothermia. By immersing them in ice water, large patients may be cooled in relatively short periods of time. A collapsible tub has been devised whereby immersion cooling takes place on the operating table, thus eliminating the necessity of shifting the patient from the bathtub to the operating table.

While cooling by immersion is rapid, certain undesirable features are associated with it. Since the fall in temperature is fast, the downward drift of the patient's temperature after he is removed from the tub is greater than that which occurs with slower methods of cooling. In some cases the drift may be greater than had been anticipated, and the temperature may fall lower than is desirable or necessary, occasionally dropping to dangerously low levels. The incidence of ventricular fibrillation has been reported to be greater with tub cooling than with slower methods of cooling. Peripheral neuritis has been noted in some patients who were immersed for periods longer than 45 minutes. Even the appearance of a patient in a bathtub in the operating room is esthetically unattractive to some individuals.

Blanket cooling, employing the Therm-O-Rite equipment, offers certain advantages over tub cooling. The temperature falls more slowly, and drift is more predictable and more easily controlled. Therefore, the danger of ventricular fibrillation is less. The time required for cooling is quite satisfactory for children and small, thin adults. However, in large or obese adults, more than 2 hours may be required to lower the rectal temperature to 30 degrees C., even when supplemental ice packs are used. The collapsible tub was devised in an effort to combine the better features of blanket and tub cooling and to achieve rapid yet safe cooling in adult patients.

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DESCRIPTION

The tub is fashioned from a large sheet of heavy plastic material which is folded with box-like corners to conform to the width and length of the operating table (Fig. 1). The margins of the sheet are reinforced and are perforated with metal awning grommets at 6 inch intervals. To support the corners and sides of the tub, upright stainless steel posts are fitted into the sliding brackets which are standard equipment on the sides of most operating room tables. After the plastic sheet has been folded into the shape of the tub, ¼ inch stainless steel rods are threaded through the grommets and through holes in the upright posts, thus forming a rigid frame for the tub. A slight modification is required at the head of the table since the adjustable head rest does not have sliding brackets to admit upright posts. However, the standard ether screen, which is an angled metal rod, may be adjusted so as to support the upper end of the tub. Ordinary test tube clamps are easily adapted to join the metal rod frame to the ether screen. The patient is placed upon the operating table with the plastic sheet in the proper position beneath him. Following induction of anesthesia, the supporting frame is fitted into place, and the sides of the sheet are raised and folded to form a tub. The tub is filled with water at room temperature. After a few minutes, ice cubes are gradually added to bring the temperature of the water down to 4 degrees C. When the desired rectal temperature has been reached, the water may be removed by unfolding a bottom corner of the sheet and permitting the water to run out into buckets. This is facilitated by raising the head of the table and tilting it slightly to one side. After the tub has been emptied, the metal frame and

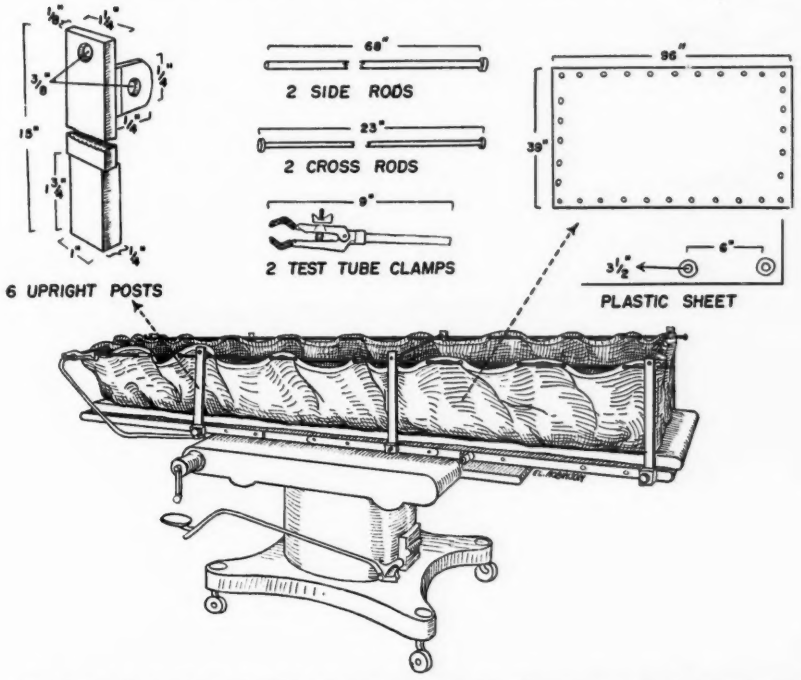

FIG. 1. Artist's sketch of collapsible tub and operating table. Measurements are for the standard operating table and a tub large enough to accommodate the average adult. The upright posts and rods are of stainless steel. The sheet is of heavy plastic or rubber.

posts are removed. It is not necessary to remove the plastic sheet which hangs down on either side of the table and is out of the way during the operation. Prior to operation it is advisable to dry the patient very thoroughly and to mop up any small puddles between the patient and the sheet. For rewarming at the conclusion of the operation, the tub may be reassembled and filled with warm water.

The Therm-O-Rite blankets can be easily used in conjunction with the collapsible tub. This may be accomplished in two ways. The bottom adult blanket will fit on the operating table beneath the plastic sheet which is thin enough so that it does not prevent the passage of heat between the patient and the blanket. A more direct method that permits somewhat better heat exchange is to place the blanket in the tub rather than under it. Two child-size Therm-O-Rite blankets have been found to fit exactly in the bottom of the tub when connected end-to-end (Fig. 2). In this manner the Therm-O-Rite equipment may be used to supplement tub cooling or rewarming of the patient.

DISCUSSION

This method of tub cooling is not advocated for use with children or small patients if blanket or ice bag cooling is rapid and easily controlled. Its greatest value is the reduction in time required to cool large or obese patients.

The initial delay between the time that cooling is started and the time that rectal temperature begins to fall has been referred to as the "temperature barrier." This barrier is the result of intense peripheral vasoconstriction when the body is first exposed to cold. Later, when the vasoconstriction is replaced by vasodilation, the barrier is passed and cooling progresses. Initial tub cooling in adult patients shortens this early latent period.

The hazard of ventricular fibrillation may be

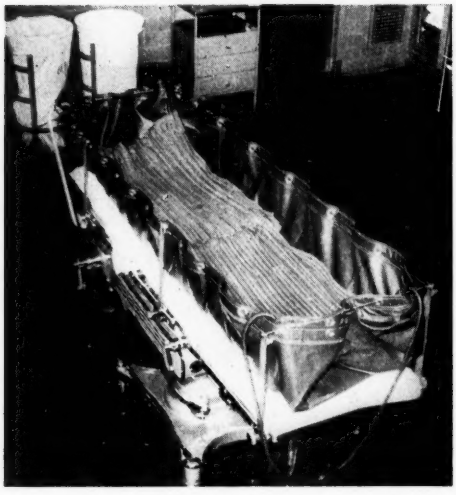

FIG. 2. Empty tub illustrating the use of the small Therm-O-Rite blankets within the tub.

reduced by starting the cooling process with water at room temperature rather than immersing the patient in an icy bath. Should ventricular fibrillation develop during cooling, the surgeon is in a much better position to open the chest while the patient is in the tub on the operating table, than he would be if the patient were in an old-fashioned bathtub on the floor. The water can be emptied quickly and the sides of the tub lowered in an instant. There is no need to move the patient from a tub to the operating table. Resuscitation of the heart may be started without delay.

By combining tub and blanket cooling, it is possible to control drift more accurately than by tub cooling alone. The temperature barrier is overcome more quickly with immersion cooling. Once the temperature of the patient has started downward and has dropped 3 or 4 degrees centigrade, the change may be made easily from tub to blanket cooling. The operation may be started while blanket cooling is in progress. Should the extent of the drift be underestimated, warm water can be circulated through the blankets. A second Therm-O-Rite machine standing by with the temperature of the solution at 46 degrees C. makes the switch from cold to warm quite easy.

The collapsible tub has been used to cool 14 adult patients. Many of these have been neurosurgical patients in whom occlusion of the arterial supply to the brain permitted successful treatment of vascular anomalies and tumors. For the patient who does not have heart disease, tub cooling has proved quite satisfactory. There has been no instance of ventricular fibrillation as a result of tub cooling, nor have there been any cases of frostbite to the extremities or peripheral neuritis. The only serious complication was a third degree burn in the sacral area which occurred during the rewarming process owing to an error in regulation of the temperature of the fluid circulating in the blankets.

This collapsible tub is not available commercially. However, the metal parts can be easily produced in any machine shop. Any type of heavy plastic or even rubber sheeting can be used. An awning maker can supply the metal grommets and stitch down the folded edges of the sheet. With simple modifications, the tub should be adaptable to most operating room tables.

SUMMARY

By means of a simple collapsible tub, immersion cooling and rewarming may take place without the necessity of moving the patient from the operating table. In combination with blanket-cooling, the induction of hypothermia is relatively rapid and drift can be controlled. In 14 clinical cases there were no instances of ventricular fibrillation and the only complication was a sacral burn which occurred during rewarming.

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Reviews of New Books

IN SPITE OF the voluminous literature on the subject of undescended testes there still remains a good deal of uncertainty as to its etiology and also its treatment. It is with the object of attempting to dispel this confusion that *Cryptorchism*[1] by Charny and Wolgin has been written.

The authors, apparently men of wide experience in this field, have dealt thoroughly with all phases of the subject—etiology, pathology, clinical symptoms, diagnosis, and treatment—and in each chapter there is an extensive review of the literature, followed by a comparison of the prevailing opinions of other writers with their own views. This is followed by a brief résumé or summary, which has been boiled down from a large volume of data in a form readily grasped by the reader.

As I see it, the difference between this book and most other publications on this subject lies in the fact that the opinions expressed and the conclusions reached by the authors are based on the study of histologic sections taken by testicular biopsy and not on impressions gained by the gross appearance and the anatomic change in position of the testis. Unfortunately, not a word is written by way of description of the technique of these many biopsies, nor is there any intimation of possible complications that may have arisen as sequelae of these procedures. The authors have throughout this work attempted to correlate the microscopic appearance of the gland with its probable function, whether it be in the discussion of the normal testis in its various stages of development, the undescended testis before and after hormonal therapy, or the scrotal testis, whether it arrived there normally, was assisted by the possible aid of gonadatropin, or was brought down surgically by means of orchiopexy. In other words, the authors have judged the entire value of any form of treatment in the light of functional rather than anatomic changes, an approach to the problem which, of course, seems entirely reasonable.

When I had completed the study of this book I was left with certain definite impressions: (1) It is quite likely much of the literature having to do with results of treatment is unreliable, because unquestionably many cases from which data have been gathered were those of pseudocryptorchism rather than true undescended testes. (2) Basically, there are two main types of undescended testis. In one, the testis is "intrinsically sick," is part of a general endocrine disturbance, cannot be expected to respond well to hormonal therapy, and will not improve functionally by operation. In the other, the testis is potentially normal, is hindered in its development by an unfavorable environment, is blocked in its descent by mechanical factors, and should improve functionally if properly brought into the scrotum by a sound surgical procedure. (3) The optimum time for consideration of either hormonal or surgical treatment is shortly before puberty, probably between the ninth and twelfth year. (4) It is quite possible that many favorable results of hormonal therapy have been in patients in whom the testis would have eventually reached the scrotum if not treated at all. (5) The undescended testis in some instances may be accompanied by local pain, may be complicated by a congenital indirect inguinal hernia, may be associated with marked psychic disturbances due to an empty undeveloped scrotum, or may present local evidence of beginning malignant change. Any of these might reasonably be considered a good indication for operation. (6) Results of treatment, favorable or otherwise, must be based on proved fertility in cases of bilateral cryptorchism, and on the microscopic histologic appearance of the gland from biopsy specimens in cases in which the abnormality is unilateral. (7) If the decision is made to resort to operation the work must be done by a surgeon whose technical skill is above average, who understands the importance of a high retroperitoneal mobilization of the two components of the spermatic cord sufficiently to shorten its pathway to the scrotum, and the necessity of freeing the cord from its fibrous and muscular coverings without in any way compressing the blood supply, either through the vessels accompanying the vas or the internal spermatic artery and the pampiniform plexus. A small atrophic testis which cannot be brought into the scrotum had probably best be removed if it is unilateral. (8) The most encouraging single publication to date from the standpoint of the surgeon appeared in 1956 (*J. Am. M. Ass.*, 160: 634) when Robert E. Gross and T. C. Jewett of Boston reported an acceptable fertility of 79 per cent in 38 cases of bilateral cryptorchism in a series of 1,222 operations for undescended testis.

Inasmuch as my personal knowledge of this subject has been materially enhanced by the study of this

[1] CRYPTORCHISM. By Charles W. Charny, M.D., and William Wolgin, M.D. 140 pages, 28 illustrations. $5.85. New York: Paul B. Hoeber, Inc., 1957.

book I do not hesitate to recommend it highly to all pediatricians, general practitioners of medicine, and particularly to the urologists and general surgeons.

—*Edwin M. Miller.*

A MOST INTERESTING and comprehensive report[2] on medical effects of the atomic bomb in Hiroshima and Nagasaki has been published as one of a series of accounts of research work performed under the auspices of the Manhattan Project and the Atomic Energy Commission. The publication is based upon a six volume report of the Joint Commission for the Investigation of the Effects of the Atomic Bomb in Japan with detailed physical data, charts, photographs, and photomicrographs. The various sections describe the scope of damage and effects on medical care and facilities of the two separate bombs, the number and types of casualties, clinical observations, reports of hematology studies, and the pathology of the atomic-bomb injuries with particular reference to specific organ damage. Attached are a series of appendices on methods employed in the surveys and a bibliography of reports made by Japanese scientists and physicians.

Much of the material included in the text has been heretofore either classified or relatively inaccessible to workers not involved in specific projects related to problems of radiation injury. In addition to its value from the historical standpoint and as a reference source the book is extremely readable and should prove most stimulating and informative to the average physician. Oughterson and Warren are to be congratulated on their painstaking efforts in making generally available the results of several years of clinical study and statistical analysis which should do much to remove the mystery surrounding thermonuclear experimentation and the current aura of popular hysteria.

—*T. G. Blocker, Jr.*

OUR ORIGINAL CONCEPTS of pharmacologic action of muscle relaxants have been undergoing substantial changes in recent years. A wealth of publications dealing with this subject has been appearing continuously. Unfortunately, some of them have brought mainly confusion to an already complicated problem.

The small volume, *Muscle Relaxants in Anesthesiology*[3], finds a way out of this confusion and presents the problems step by step in an orderly and understandable fashion. Simplicity of language and clarity of style help a great deal in this difficult task.

Foldes has been actively interested in both the experimental, as well as the clinical, aspects of the problems of muscle relaxants and has written numerous articles on this subject. His book is divided into two main parts. The first part deals with basic problems in its 5 chapters: (1) "History and Experimental Groundwork"; (2) "Chemistry of Muscle Relaxants"; (3) "Physiology of Neuromuscular Transmission"; (4) "Neuromuscular Block"; (5) "Pharmacology of Muscle Relaxants." In these chapters the present concepts and theories are clearly explained. A few simple diagrams help greatly in the understanding of the problems presented. A thorough study of this part of the book is necessary if one is to derive the most benefit from the clinical part.

The clinical part of the monograph is divided into 7 chapters. In these chapters there are detailed explanations of the administration, complications, and antagonists of muscle relaxants. Those most frequently used in todays' practice are treated in a separate chapter. Miscellaneous and special uses in specific diseases and syndromes are given particular consideration. The last chapter summarizes the most important clinical aspects and emphasizes safeguards for correct use of muscle relaxants.

An extensive bibliography of American, as well as foreign, literature includes most of the important contributions. The book is well made, and is printed in large readable type on nonglossy paper. Its format is small enough to fit an average coat pocket.

In summary, this book contains a wealth of current information and brings up to date a complicated yet highly interesting subject.

—*Jan J. Kukral.*

THE BOOK, *La douleur et les douleurs*[4] is the summary of a symposium on the subject of pain, held in Paris in 1955. Its 22 contributors include such well known persons as G. Boudin, Macdonald Critchley, R. Garcin, J. Lhermitte, J. Sherrer, and R. Thurel, and it is published under the direction of Th. Alajouanine. The introductory chapter is among the last of René Leriche's writings, and is published posthumously.

This symposium approaches pain as a physiologic entity, and the painful states as clinical syndromes to be understood pathologically and therapeutically. It is constantly pointed out that the whole subject of pain must be approached from different points of view, depending upon whether one's interests are centered upon symptomatology, nosology, or physiopathologic interpretation. Indeed, Leriche asks the question: "What really is pain"? It can be "explained," he says, if the problem is viewed in its totality, as a phenomenon essentially functional in nature, varying as the physiologic conditions of the nervous system vary, which is to say, he adds, that we do not know what pain is, and that it is indefinable. In a review of the physiology of the various levels of the sensory system, and of the manner in which the psyche may interplay with these organs of the soma to produce what are known as painful responses, many both practical and philosophic questions are raised in this book; by no means are all of these questions answered. For this reason, particularly, the book is provocative of thought.

With free use of English, American, and French references, there are excellent reviews of the pain of various systems (as the muscular, cutaneous), together with discussions on the physiology, pathology, and treatment of such entities as visceral, vascular, and causalgic pain, the specific neuritides (trigeminal), headache in its many and varied forms, and hallucinatory pain (as amputation phenomena). J.

[2]MEDICAL EFFECTS OF THE ATOMIC BOMB IN JAPAN. Edited by Ashley W. Oughterson and Shield Warren. 1st ed. 477 pages, illustrated. $8.00. New York, Toronto, London: McGraw-Hill Book Co., Inc., 1956.

[3]MUSCLE RELAXANTS IN ANESTHESIOLOGY. By Francis F. Foldes, M.D. Illustrated by Margaret M. Croup. 210 pages, illustrated. Springfield: Charles C Thomas, 1957.

[4]LA DOULEUR ET LES DOULEURS. Publication was under the direction of Pr. Th. Alajouanine, with 22 collaborators. 346 pages, 16 illustrations. 2,400 fr. Paris: Masson et Cie, 1957.

Lhermitte specifically warns against the use of mutilating operations upon the brain, cord, and nerves in any form of hallucinatory pain.

There is a very interesting chapter on "moral pain," by J. Morlaas, in which the author points out that this peculiar condition, hard to define, difficult to "demonstrate experimentally," but none the less most real to the victim, is apparently the result of voluntary or freely conducted acts during the normal course of living, but ending, through an innate faultiness in the patient, in melancholy and depression, even feelings of guilt. There is such distortion of moral sense that the patient can no longer judge his acts and their consequences, but can only feel the pain, the awful finality, of the (to him) greatly exaggerated moral upheavals and reversals in his life. Perhaps, states the author, this innate faultiness is the victim's instrument of relationship with society, and his "pain" probes the depths of his social life. The author does not think that moral pain is the result of a loss of will to live, or taedium vitae.

The last 2 chapters are concerned with the pharmacodynamics of pain and of the various, and usually far short of satisfactory, neurosurgical measures available for the relief of pain. The book is neither indexed nor adequately illustrated. —*John Martin.*

THE MANY TUMORS of the pericardium, heart, blood vessels, and lymphatic vessels are covered in a systematic fashion in Fascicle 7 in the *Atlas of Tumor Pathology*.[5] All the tumors are well described and carefully illustrated with pictures of superb technical excellence. The only exceptions to this are some of the photographs of gross specimens which are not particularly informative, for example, Figures 46, 59, and 60. The illustrations of patients showing the clinical appearances of the tumors are, however, excellent. This fascicle is a most welcome addition to the *Atlas of Tumor Pathology* and will establish itself as a standard reference on the subject.

One of my colleagues divides authors into two groups: "lumpers" or "splitters." Dr. Castleman obviously belongs to the former group and his presentation brings order out of chaos. Fascicle 19 is a model of lucidity and conciseness. The difficulties of classification and diagnosis of hyperplasia and tumors of the thymus gland are clearly presented and resolved. The black and white illustrations, especially the photomicrographs, are technically superb and very instructive. The use of charts and diagrams is also most helpful. Some of the color illustrations do not do justice to the original photographs but this is a minor fault indeed in an outstanding treatise.

—*William B. Wartman.*

OBSERVATIONS made from 1942 to 1945 are reported in *Orthopedic Surgery in the Mediterranean Theater of Operations*.[6] Early in 1944 specific practices had been established for the management of open fractures. Later these principles were applied to open wounds of the joints.

By utilization of consultants and interchange of personnel, the treatment of extremity injuries steadily improved. Documentation was not complete in all casualties. Those specially followed from injury to healing served as the basis for the conclusions in this work.

At the outset, compound battle fractures were cared for by several methods, including closed plaster treatment and open treatment. Delayed primary closure of wounds followed after considerable study and experiment. An important factor for success was careful and meticulous initial débridement shortly after injury. The most frequent cause of failure was inadequate surgical treatment at this stage. Antibiotics were of help in preventing systemic reactions and cellulitis in cases of incomplete surgery. Blood replacement was an essential factor in resuscitation.

At the primary operation, bone without soft tissue attachment was removed. Although free bone could serve as a graft the hazard of infection in devitalized bone offset this advantage.

With adequate initial treatment there was little suppuration or necrosis. Delayed primary closure was best accomplished between 4 and 7 days after the injury, but was done as late as 10 days. Injuries about the foot and ankle did not lend themselves to delayed primary closure because there is little maneuverable soft tissue in this area.

Wounds were sutured without tension. Buried sutures were kept to a minimum. Bones that could be covered with considerable soft tissue were often fixed with screws, wires, or plates. The desired site for application of internal fixation was through another incision to permit covering the metal with normal soft tissues. Open fixation of the tibia, especially with plates, led to severe sequestration of bone in many cases. Some of these tibias healed after removal of plates and screws. Massive sequestration was not found after screw fixation or wiring.

External skeletal fixation with different types of pins and fixation apparatus was not satisfactory. Apparatus did not hold up well in transit. Infection about pins was frequent. Intramedullary fixation was not available at that time.

The treatment of open wounds of the knee and hip joint and of the smaller joints was based on the same principles as that of open fractures. Excision of devitalized portions about the joint, such as the knee, with massive irrigation and closure of the synovia, was often successful and could be followed by delayed primary closure. The joints which developed sepsis after initial primary surgery were usually those with inadequate drainage and inadequate débridement. Wide excision of joints, as practiced in the French Army, was not popular, however, among American surgeons.

[5] ATLAS OF TUMOR PATHOLOGY. Section III—Fascicle 7, TUMORS OF THE CARDIOVASCULAR SYSTEM. By Benjamin H. Landing, M.D., and Sidney Farber, M.D. 138 pages, 138 illustrations, $1.50. Section V—Fascicle 19, TUMORS OF THE THYMUS GLAND. By Benjamin Castleman, M.D. 83 pages, 81 illustrations and 4 color plates. $1.00. Published by the Armed Forces Institute of Pathology under the auspices of the Subcommittee on Oncology of the Committee on Pathology, National Research Council. Washington, D.C.: Armed Forces Institute of Pathology, 1955, 1956.

[6] SURGERY IN WORLD WAR II. ORTHOPEDIC SURGERY IN THE MEDITERRANEAN THEATER OF OPERATIONS. Edited by John Boyd Coates, Jr., M.C., Mather Cleveland, M.D., and Elizabeth M. McFetridge, M.A. 368 pages, illustrated. Washington, D. C. Office of the Surgeon General, 1957.

The principles of delayed primary closure were not adapted to amputations, in deference to the Surgeon General's directive regarding circular type amputation with spontaneous closure by traction.

Certain noncombat orthopedic lesions involving the back, feet, knee, dislocations of the shoulder, and fractures of the carpal scaphoid are discussed in this volume. —*Kenath H. Sponsel.*

THE PURPOSE of the volume entitled *The Principles and Methods of Physical Diagnosis*[7] might best be stated by quoting from the author's first paragraph in the preface to the second edition; " . . . for some years it has been my privilege to act as one of the guest examiners when the American Board of Internal Medicine conducts oral examinations in Philadelphia. In this capacity, I have frequently been disturbed by the incompetence in physical examination shown by a number of otherwise qualified candidates for certification, all of whom had passed the written examination."

In addition to the usual chapters devoted to history taking and the technique of physical examination of the various regions of the body, this volume is noteworthy in that it includes a short chapter on the "Psychiatric Survey," a chapter entitled "Sounds from the Thorax; Acoustic Principles," and a chapter on the "Pediatric Examination." The general format is attractive, the paper stock is of good quality, there are many illustrations, and the size, approximately 6½ by 9¼ by 1 inch, is convenient.

Chapter 1 is entitled "The History" and contains the principles of history taking together with an outline for doing a physical examination. Chapter 2, entitled "Psychiatric Survey," is a concise presentation of some of the basic concepts of psychiatric evaluation. This may be somewhat advanced for first or second year medical students, but serves to give orientation in this regard. The chapter on "Examination of the Head" covers the routine physical examination of the scalp and face, and is generously illustrated, with some excellent color plates showing cancer of the oral cavity. The chapter on "Examination of the Breasts" is noteworthy because of a section on self-examination as well as fairly detailed descriptions of proper technique in examination and illustrations of lesions frequently encountered. Chapter 8 was written by S. Reid Warren, Jr. and is a review of the basic physical principles related to the production and transmission of sound. It is an attempt to stimulate the student to correlate acoustic phenomena from the viewpoint of physical and diagnostic theory. The next 4 chapters are devoted to the technique of examination of the chest. These are followed by descriptions of techniques for examining the circulatory system, which include some of the common congenital cardiac abnormalities, and by illustrations of angiocardiograms. The chapter devoted to the abdomen is quite complete. The chapters which follow on the gynecologic examination and the male genitalia, anus, rectum, and rectosigmoid colon are also quite thorough. The last chapter in the book is a fairly detailed consideration of the pediatric examination.

Special examinations, such as those devoted to the hands, are of necessity very briefly described. In fact, most of the description devoted to examination of the upper extremity is included in the chapter on the neurologic examination. Incidentally, it is here that one of the inevitable errors creeps in, as an illustration of wrist drop is attributed to paralysis of the median nerve.

In summary, it is the reviewer's opinion that the volume is a compact, thorough, well illustrated text devoted to physical diagnosis.—*John H. Schneewind.*

THE VOLUME entitled *The Specialities in General Practice*[8] is in its second edition, the first having appeared in 1951. The Editor, Russell L. Cecil, has engaged outstanding men in each specialty to contribute to the book. It has been designed to serve as a convenient, brief, and ready reference for the general practitioner in the management of some of the less serious problems within the specialties.

The first section of the volume is concerned with minor surgery. An excellent series of diagrams and figures bring out important details in the management of common office procedures and minor surgical problems. The text complements the figures and diagrams in a concise manner, and the fundamental principles underlying the surgical procedures described are emphasized.

The section on orthopedic surgery is one of the longer segments of the volume and its value is commensurate with its length. Here again, the author has used a generous number of figures, diagrams, and roentgenograms to illustrate the common orthopedic and traumatic conditions seen in this type of practice. Precise as well as concise in its text, the section is outstanding in its clarity and completeness. The basic rationale of the use of many orthopedic procedures is explained on logical grounds. Little or no controversial material is included. In these relatively few pages the author has managed to give a kaleidoscopic view of the orthopedic surgeon's practice, giving sound basic information and advice on every page.

The section on urology suffers somewhat because of the lack of diagrams describing how simple urologic procedures can be performed. There are, however, reproductions of representative surgical specimens unfortunately not often seen in a general practice. The descriptions of infections of the urinary tract and their treatment are excellent and are presented in some detail throughout the section.

The section devoted to diseases of the anus, rectum, and colon is a most valuable one. The oftentimes forgotten simple maneuvers in the management of anorectal conditions are explained by means of the written text, photographs, and diagrams. The author has made every effort to cleave to simple lines in his descriptions of disease processes and operative pro-

[7]THE PRINCIPLES AND METHODS OF PHYSICAL DIAGNOSIS; CORRELATION OF PHYSICAL SIGNS WITH CERTAIN PHYSIOLOGICAL AND PATHOLOGICAL CHANGES IN DISEASE. By Simon S. Leopold, M.D. 2nd ed. With a chapter on Sounds from the Thorax; Acoustic Principles by S. Reid Warren, Jr., Sc.D. in E.E. 537 pages, 379 illustrations, and 25 colored plates. $9.00. Philadelphia and London: W. B. Saunders Co., 1957.

[8]THE SPECIALITIES IN GENERAL PRACTICE. Edited by Russell L. Cecil, M.D., and Howard F. Conn, M.D. 2nd ed. 780 pages, 76 illustrations. Philadelphia and London: W. B. Saunders Co., 1957.

cedures. The demonstration of simple surgical techniques performed as office operations are well shown by clear-cut diagrams and the descriptive text. The author has included an excellent section on traumatic wounds of the large bowel.

The section on gynecology is unfortunately short. The material covered is exceptionally well done and well illustrated. Since gynecology represents a considerable segment of a general practice, it is unfortunate that descriptions of more of the simple office gynecologic procedures were not included in this section of the volume. In the interest of brevity, the author has perhaps sacrificed the completeness of his subject.

The portion of the volume dealing with obstetrics, however, is well managed with clarity and completeness. Here, the descriptive diagrams and figures are most helpful in the understanding of the text. The management of normal, as well as abnormal, deliveries is described and postpartum complications are discussed at considerable length. This is an excellent section of the volume.

The section on pediatrics should be most helpful to those who are in particular need of information of this type. This section describes the methods of immunization and what can be expected from each of them. This chapter is quite long; each of the topics discussed is covered with considerable detail with the intent of describing these conditions as they occur in childhood as distinct from the same conditions in adults.

The chapter on ophthalmology presents a series of topics, each described concisely, which should be of value to all practitioners of medicine. A series of photographs in color illustrate conditions of the eyes and eyelids often seen by physicians. The remainder of the section describes in considerable detail the most important diseases of the eye and the management of them. The same comments can be made upon the section devoted to the nose and throat. The most important anatomic, radiologic, and physiologic aspects of the nose and throat are discussed and the application of these principles to the treatment of rhinologic disease is very well done.

The section on diseases of the larynx, bronchi, and esophagus is outstanding. The author has described in detail the many diseases and malformations associated with the larynx, bronchi, and esophagus. Diagrams, reproductions of roentgenograms, illustrations of endoscopic procedures, and descriptions of the anatomy of the lungs and mechanics of respiration are included. The mechanism of valvular obstruction which produces emphysema, and techniques for the removal of foreign bodies are also discussed. This section is complete in every detail and perhaps suffers only by the minor consideration of the lack of colored plates in the description of the endoscopic views of bronchiogenic carcinoma or other endoscopic views of the esophagus.

The section on otology is nicely managed, both with respect to the anatomic and physiologic aspects, and also to the treatment of diseases related to the ear. The simple descriptions and the use of representative plates and diagrams are most effective.

The chapter on dermatology and syphilology is excellent, except for the fact that the illustrations of the various types of dermatologic disease are not reproduced in color and have, therefore, lost much of their teaching value. The field of dermatology, however, is well covered in this section and many helpful hints concerning treatment are included.

Similar remarks can be made about the section on psychiatry. The author has presented briefly and concisely some of the more common mental conditions encountered by a general practitioner. This section would serve admirably for the busy doctor, since it contains few, if any, controversial aspects of psychiatry but does describe rather well the more common difficulties that a general practitioner would be asked to treat.

It is easy to understand why the first edition of *The Specialities in General Practice* was received with such enthusiasm. In the preface to the volume, Dr. Cecil mentions that he has constantly kept in mind the needs of the general practitioner. He has admirably fulfilled his goal. The reviewer would like to add that the volume is also of value to the specialist, regardless of his field, since problems of other types than his own specialty are constantly present in any type of office practice. —*Orville F. Grimes.*

THE SECOND EDITION of *Surgery of the Biliary Tract, Pancreas, and Spleen*,[9] one of a series of handbooks of operative surgery, conforms to the intentions of the author and publishers in presenting a subject in a concise manner. There is no intent to cover in complete detail the problems of anatomy, physiology, pathology, and diagnosis, but, sufficient information is given to lead one into the operative field. There are many good, simple, understandable illustrations, and the author and artist must be commended.

It is pleasing to read the opening chapter which emphasizes that the careful taking of a history in patients with diseases of the gallbladder, pancreas, and spleen gives the most valuable diagnostic information. It is the detailed interrogation of the patient that counts, a matter which is appreciated more as experience mounts.

In the section on liver diseases the author describes the simple technical procedures in an excellent manner; complicated procedures are also well covered. The reviewer believes that the technical aspects of the management of surgical conditions of the liver are better handled than in most texts. It is comforting to read that the author believes 5 millimeters is a safe distance for transecting the cystic duct from the common duct. In recent years several authors have been advocating transecting the duct about 2 millimeters from, or even practically flush with the common duct, and in inexperienced, as well as experienced, hands this can lead to postoperative common duct strictures. The author criticizes the routine use of a long arm T tube, with which many are in agreement. Postoperative choledochograms are discussed but are not routinely recommended. Many disagree with this and believe they are a "must" in every patient who has had

[9] SURGERY OF THE BILIARY TRACT, PANCREAS, AND SPLEEN; A HANDBOOK OF OPERATIVE SURGERY. By Charles B. Puestow, M.D., Ph.D.(Surg.). Illustrated by Jessie W. Phillips. 2nd ed. 381 pages, illustrated. $9.75. Chicago: Year Book Publishers, Inc., 1957.

a choledochostomy and if a T tube or catheter has been placed in the common duct. There is an excellent description of the operative procedure for repair of the common duct which is a good review for every surgeon.

The section on diseases of the pancreas emphasizes conservative treatment for pancreatitis unless there is doubt as to the diagnosis. If an operation is done, there should be minimal surgery and trauma of the pancreas and no other surgery should be done unless definite pathologic changes are present. The author recommends routine drainage of the peritoneal cavity. He gives an excellent description of the technique for ductal drainage of the pancreas, and emphasizes retrograde pancreaticojejunostomy rather than sphincterotomy for chronic pancreatitis. With enlargement of the head of the pancreas suggesting carcinoma of the pancreas, a radical pancreaticoduodenostomy is not recommended unless the result is positive at biopsy. The author supports his contention by the statement that not infrequently short circuiting operations have given good results, thus establishing the possibility of a wrong diagnosis in this serious situation. A radical resection should never be done with metastasis or extension of the disease.

There is no bibliography and practically no mention of authors who have been originators or proponents of the operations described. This makes for easy reading and a quick pick-up of possible procedures in a given situation but at the expense of not giving the reader a review of the development of these particular fields of surgery. —*Russell Best.*

BOOKS RECEIVED

Books received are acknowledged in this department, and such acknowledgment must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interests of our readers and as space permits.

CARDIOVASCULAR COLLAPSE IN THE OPERATING ROOM. By Herbert E. Natof, M.D., and Max S. Sadove, M.D. Foreword by Warren H. Cole, M.D. 197 pages, illustrated. $6.00. Philadelphia and Montreal: J. B. Lippincott Co., 1958.

OPERATIVE SURGERY. Edited by Charles Rob, M.C., M.Chir., F.R.C.S., and Rodney Smith, M.S., F.R.C.S. Vol. V—ORTHOPAEDIC SURGERY. 371 pages, illustrated. London: Butterworth & Co., Ltd., 1957.

DER VARIKOESE SYMPTOMEN-KOMPLEX; MIT SEINEN FOLGEN UND NACHKRANKHEITEN UNTER BESONDERER BERUECKSICHTIGUNG DER FEHLERQUELLEN IN DIAGNOSTIK UND THERAPIE. By Priv. Doz. Dr. Friedrich Pirner. 267 pages, 82 illustrations. Stuttgart: Ferdinand Enke, 1957.

FRUEHERKENNUNG UND BEHANDLUNG DES WEIBLICHEN GENITALCARCINOMS. Edited by Prof. Dr. Dr.F.v. Mikulicz-Radecki. 182 pages, 46 illustrations, 16 in color. Stuttgart: Ferdinand Enke, 1957.

TUMORS OF THE SOFT SOMATIC TISSUES: A CLINICAL TREATISE. By George T. Pack, M.D., LL.D., F.A.C.S., and Irving M. Ariel, M.D., F.A.C.S., with 15 collaborating authors. 820 pages, 652 illustrations. $30.00. New York: Hoeber-Harper, 1958.

THE EARLY DIAGNOSIS OF THE ACUTE ABDOMEN. By Sir Zachary Cope, M.D., F.R.C.S.(Eng.). 11th ed. 188 pages, illustrated. $4.50. London, New York, and Toronto: Oxford University Press, 1957.

GYNECOLOGIC AND OBSTETRIC PATHOLOGY; WITH CLINICAL AND ENDOCRINE RELATIONS. 4th ed. By Emil Novak, M.D., D.Sc.(Hon.), F.R.C.O.G.(Hon.), and Edmund R. Novak, M.D. 650 pages, 683 illustrations, 25 in color. $14.00. Philadelphia and London: W. B. Saunders Co., 1958.

EL DOLOR EN GINECOLOGIA. By Manuel Usandizaga, Emilio Gil Vernet, and Emilio Molinero. 198 pages, illustrated. Barcelona: Vergara Editorial, S. A.

EL RIÑÓN PELVIANO EN LA MUJER. By Manuel Usandizaga. 142 pages, illustrated. Barcelona: Vergara Editorial, S. A.

ENDOCRINOLOGIA GLANDELOR SALIVARE. BIBLIOTECA MEDICALA V. By Acad. C. I. Parhon, A. Babes, and I. Petrea. 318 pages, illustrated. Bucuresti: Editura Academiei Republicii Populare Romine, 1957.

ANESTEZIA PROBLEME TEORETICE SI PRACTICE. BIBLIOTECA MEDICALA VI. By Acad. Nicolae Hortolomei, Voinea Marinescu, Dan Setlacec, and George Litarczek. 798 pages, illustrated. Bucuresti: Editura Academiei Republicii Populare Romine, 1957.

SPINAL ANESTHESIA. By John B. Dillon, M.D. 61 pages, illustrated. $3.00. Springfield, Ill.: Charles C. Thomas, 1958.

PATHOLOGIE ET CHIRURGIE DES CAROTIDES. By Professor Georges Arnulf. 544 pages, 154 illustrations. 6.800 fr. Paris: Masson et Cie, 1957.

DUODÉNUM ET PANCRÉAS. Under the direction of Guy Albot and Félix Poilleux. Actualités hepatogastro entérologiques de l'Hotel Dieu 1956. 269 pages, 126 illustrations. 3.500 fr. Paris: Masson et Cie, 1957.

TRAITEMENT CHIRURGICAL DE LA RECTO-CÔLITE ULCÉRO-HÉMORRAGIQUE. By E. Delannoy and M. Martinot. 120 pages, illustrated. 1.400 fr. Paris: Masson et Cie, 1957.

TECHNIQUE CHIRURGICALE INFANTILE. By Professeur Bernard Duhamel, in collaboration with Simone Segaux. 354 pages, 289 illustrations. Paris: Masson et Cie, 1957.

ABDOMINAL OPERATIONS BY THE VAGINAL ROUTE. By Paul Werner, M.D., and Julius Sederl, M.D. Translated by L. M. Szamek, M.D. With a foreword by Richard W. Te Linde, M.D. 165 pages, 120 illustrations. $9.00. Philadelphia and Montreal: J. B. Lippincott Co., 1958.

RADIUM-ISODOSEN DIE RADIUMDOSIERUNG IN "R." By Dr. Med. August Verhagen. With an introduction by Prof. Dr. K. Nordmeyer. (German and English text.) 103 pages, illustrated. Stuttgart: Georg Thieme, 1958.

DIE HORMONALE BEHANDLUNG VON ZYKLUSSTOERUNGEN EIN LEITFADEN FUER DIE PRAXIS. By Dr. Med. Rolf Kaiser, with an introduction by Prof. Dr. W. Bickenbach. 54 pages, illustrated. $1.40. Stuttgart: Georg Thieme, 1958.

ULCERATIVE COLITIS. By Harry E. Bacon, M.D., F.A.C.S., F.A.P.S. Foreword by Alton Ochsner, M.D., F.A.C.S., F.A.P.S.(Hon.). With contributions by Paul T. Carroll, M.D. 395 pages, 184 illustrations. $15.00. Philadelphia and Montreal: J. B. Lippincott Co., 1958.

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